Encyclopedia of Schizophrenia

Focus on Management Options

W. Wolfgang Fleischhacker
Ian P. Stolerman
Editors

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This book consists of selections from the Encyclopedia of Psychopharmacology, 1st Edition, edited by Prof. Ian Stolerman and published by Springer Verlag Berlin Heidelberg New York in 2010.

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Preface

This mini-encyclopedia aims to provide a survey of the wide range of interventions available for treating schizophrenia at a level appropriate for non-specialists who are beginning their engagement in the area and for others whose studies lead them to seek an entrée to the field as well as a source of reference for the specialist. The pharmacological options are considered alongside psychosocial management approaches and the advantages and disadvantages of each treatment modality are outlined. The entries are written by leading experts, including basic and clinical scientists in academia and industry, and include descriptions of many relevant fundamental psychological and biological processes of the disorder. The volume owes much to the Encyclopedia of Psychopharmacology edited by Ian Stolerman IP (published by Springer-Verlag in 2010), from which some entries are reproduced. Where entries deal with pharmacological interventions, the aim is to provide detailed information on the neuropsychopharmacology of the substances from domains such as clinical, experimental, and molecular pharmacology, insofar as they impact upon understanding of schizophrenia. Articles on non-drug interventions review the most recent evidence base related to commonly applied psychotherapeutic and rehabilitative measures. Other essays focus upon the key concepts and research methods used in the field, describing the main features of investigative techniques and outlining their roles, the types of information obtained and why they are needed; the advantages and limitations of a technique may also be summarized. The essays are complemented by many short definitions of important terms; in the interest of ease of reading, these definitions are not assigned to named authors; they are typically related to specific essays that they cross-reference and relevant authorship details can be found in the latter.

We thank the authors of the entries, all of whom have sustained internationally recognized records of scholarly activity in the field. The team includes individuals based in academia as well as the pharmaceutical industry, reflecting the frequent and often essential collaborations between these sectors. Their exceptional work forms the substance of the product and they have given generously of their time and expertise. It would also not have been possible to produce the book without the support of the publisher's staff who have supported the project so ably.

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Contents – Schizophrenia Key Essays

Active Avoidance

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Synonyms

Conditioned avoidance response
two-/one-way active avoidance

Definition

Active avoidance refers to experimental behavioral paradigms where subjects (mainly rodents) are trained to, following the onset of a conditioned stimulus (CS), move from a starting position to another position in the testing apparatus within a fixed amount of time (avoidance). Failure to move within the given time frame, results in the onset of a negative reinforcer, usually a weak electric shock in a grid floor, until a correct move is performed (escape). In animals performing at a high level of correct response following training, drugs that are effective as antipsychotics, but not other classes of drugs, show a unique ability to selectively suppress the avoidance behavior, within a clinically relevant dose range, while leaving escape behavior intact. Because of this robust marker for the prediction of antipsychotic activity, the active avoidance test is primarily used, and considered an important screening tool, for the detection of novel potentially ▸antipsychotic drugs.

Principles and Role in Psychopharmacology

Background

It was found early that antipsychotic drugs for the treatment of ▸schizophrenia had the ability to produce a selective suppression of active avoidance/conditioned avoidance behavior in rats (Cook and Weidley ▸2). Later, as more antipsychotic drugs came on the market, it was found that this was a unique property among antipsychotics that was not shared by other classes of pharmacological agents, and that the selective suppression of conditioned avoidance response (CAR) produced by the antipsychotic drugs correlated with their main therapeutic mechanism of action namely brain dopamine D2 receptor blockade (Arnt ▸1).

History and Procedures

The active avoidance procedure has connections back to classical conditioning (as first presented by I.P. Pavlov in, 1927) (Classical (Pavlovian) conditioning). The concept was further developed by the experimental psy-

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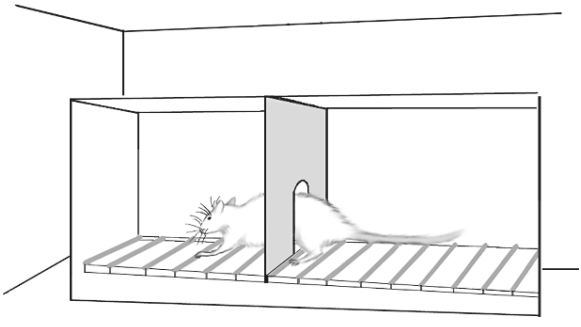
chologist B.F. Skinner. Skinner showed that a certain behavior could be maintained by the consequences it produced, and called this type of behavior operant behavior (Operant behavior in animals). Thus, operant behavior (such as active avoidance response) can be defined as behavior that is maintained by its consequences.

The basic principle of active avoidance is that an animal (usually rodent) is trained (conditioned) to make a specific response within a fixed time interval when presented with an auditory, or visual, stimulus (CS). During training, incorrect responses (i.e., late responses) will trigger a negative reinforcer (unconditioned stimulus; UCS), usually a weak electric footshock presented in a grid floor, that will be active together with the CS until a correct response occurs. Thus, the animal terminates the negative reinforcer (together with the CS) by making the appropriate response. If the response, expected to be performed by the animal, is to move from one place to another upon presentation of the CS, the procedure is said to be using the active avoidance paradigm. Active avoidance procedures using a negative reinforcer typically record three dependent variables: avoidance (correct move within stipulated time frame), escape (correct, but late, move following onset of negative reinforcer), and escape failure (failure to perform a correct move despite the onset of negative reinforcer within a certain cut-off time) (see e.g., Wadenberg et al. ▸10).

The active avoidance paradigm can be carried out mainly in two different ways: (1) one-way active avoidance; (2) two-way active avoidance. The one-way active avoidance procedure has the experimenter placing the animal in a chamber with a metal grid floor (for the electric shock, UCS), and upon presentation of the CS, the animal is required to move from the starting chamber into another (safe) compartment of the experimental box or jump onto a wooden pole hanging down from the ceiling of the box. The experimenter then has to move the animal back into the starting chamber for the next trial. In the two-way active avoidance procedure on the other hand, the animal moves back and forth (shuttles) between two compartments of equal size and appearance in the box via an opening in the partition dividing the box into the two compartments (shuttle-box) (Fig. ▸1). Here, the animal has to learn that upon presentation of the CS, it is always supposed to cross over to the other empty compartment in the box. Training and experimental sessions typically consist of a fixed number of trials over a certain time interval. The two-way active avoidance procedure has over time become the most commonly used procedure, most likely in part because this procedure can be set up as a computer-assisted apparatus with several boxes run simultaneously by one computer, thus saving time and money.



Active Avoidance. Fig. 1. The figure shows a conventional two-way active avoidance apparatus (schematic drawing by Sofia I Wadenberg).

The training phase (typically needing three to four consecutive training days) in the active avoidance paradigm can be considered an acquisition phase (i.e., acquisition of avoidance performance), while, following training, animals that perform well show retention (over time) of the acquired avoidance performing ability. Screening for novel, potentially antipsychotic drugs uses well-trained, high avoidance performing animals. The marker for potential antipsychotic activity thus is the ability of an acutely administered drug to selectively, and temporarily, suppress the retention of avoidance performance in the animals.

Evaluation and Use of the Active Avoidance Test

Animal behavioral tests (so-called animal models), used in the development of novel drugs for pharmacological treatment of diseases, are typically evaluated and rated for their fulfillment of validity criteria such as (1) predictive, construct and face validity; (2) their reliability; and (3) how they fare in terms of producing false positives or negatives. The active avoidance test is commonly considered to have high predictive validity, since all clinically effective antipsychotics, but not other classes of drugs, show the ability to selectively suppress avoidance behavior with a positive correlation between doses needed for the selective suppression of avoidance and their clinical potency for the effective treatment of schizophrenia (Seeman et al. ▸6). More recently it was also found that antipsychotics produce selective suppression of avoidance in doses that result in a brain striatal dopamine D2 receptor occupancy around 65–75% in the rat (Wadenberg et al. ▸9), which is also the percentage of dopamine D2 receptor occupancy usually needed for therapeutic response to occur in schizophrenic individuals following antipsychotic treatment. In other words, the active avoidance test identifies

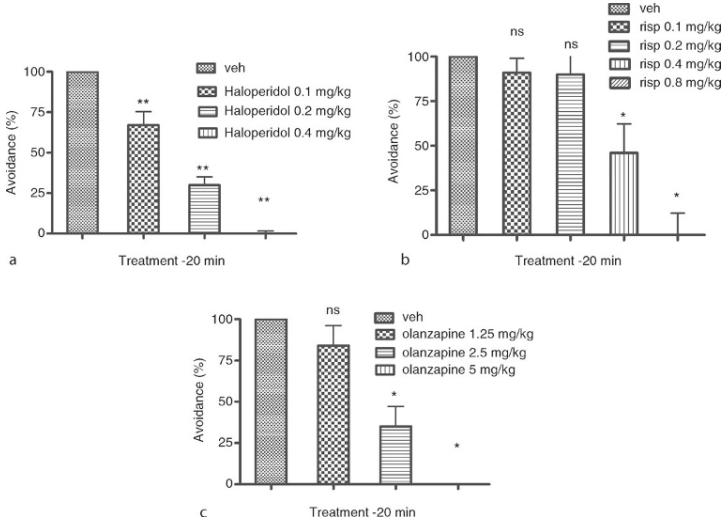
potential antipsychotic activity of new drugs tested with high predictive certainty. The active avoidance test has also been shown to have some construct validity (i.e., selective suppression of avoidance may mimic a blockade of some pathophysiological mechanisms in schizophrenia). Thus, the local application of an antipsychotic-related dopamine D2 receptor blocking agent, (-)sulpiride, into various brain areas in the rat, produced selective suppression of avoidance only when injected into the nucleus accumbens/ventral striatum (Wadenberg et al. ▸8), a brain area that has a prominent role in the dopamine mesolimbic pathway that is commonly thought to be involved in the psychotic symptoms in schizophrenia (Laruelle et al. ▸3) (Aminergic hypotheses for schizophrenia). The active avoidance test has, however, no face validity, as it does not mimic any behavioral core symptoms of schizophrenia. The active avoidance test also shows high reliability, as there is a high degree of agreement between laboratories as to which compounds produce antipsychotic-like effects and in what dose range that occurs. Finally, to the best of the Author's knowledge, the active avoidance test produces few, if any, false positives or negatives. Thus, there is no antipsychotic, known to be clinically effective, that does not produce a selective suppression of active avoidance within a clinically relevant dose range. In addition, drugs that have failed in clinical trials, or studies, for antipsychotic activity (such as for example, selective serotonin2A antagonists, selective dopamine D1 or D4 receptor antagonists) also, either showed no effect on active avoidance, or failed to produce a dose dependent suppression of avoidance without concomitant inhibition also of the escape variable (i.e., producing failures).

Based on the properties listed above, the active avoidance test falls into the category of so-called screening tests. A screening test is used by drug companies to evaluate synthesized molecules for a specific therapeutic property. When the screening test is an animal behavioral test, drug companies usually label the procedure in vivo pharmacology. Effects in these tests should occur following an acute administration of test drug, and only molecules that are effective against a particular disease should produce the specific effect that constitutes the marker for clinical activity – in this case selective suppression of avoidance within a clinically relevant dose range is produced.

The Active Avoidance Test and Identification of Drug Pharmacological Properties

There is no doubt that active avoidance behavior is strongly associated with brain dopamine neural transmission, and that the suppression of avoidance performance correlates significantly with the degree of striatal dopamine D2 receptor occupancy produced by D2 receptor blocking antipsychotic drugs. However, the active avoidance test not only identifies traditional,

mainly dopamine D2 blocking antipsychotics such as haloperidol (Fig. ▸2a), but is also equally sensitive in detecting the antipsychotic activity of the newer, so-called atypical, antipsychotics with a different mechanism of action such as combined lower dopamine D2/high serotonin2 receptor blockade (e.g., olanzapine, risperidone) (Fig. ▸2b,c), or being partial agonists at dopamine D2 receptors rather than pure D2 antagonists (i.e., aripiprazole).



Active Avoidance. Fig. 2. Shown are typical dose-response effects on active avoidance response (selective suppression of avoidance) by the typical antipsychotic haloperidol (**a**), and the atypical antipsychotics risperidone (**b**), and olanzapine (**c**) in rats. Data are presented as medians ± semi-interquartile range ($n = 6–9$).

In addition, data from clinical studies (Litman et al. ▸4; Schubert et al. ▸5) are in line with, and support, experimental data showing that the active avoidance test also reliably detects sufficient antipsychotic activity obtained by adjunct treatment with some non-D2 blocking agents (such as alpha2 adrenoceptor antagonists or acetylcholinesterase inhibitors) to a low dose of an antipsychotic not giving sufficient dopamine D2 occupancy alone to produce antipsychotic activity (Wadenberg and Karlsson ▸10; Wadenberg et al. ▸7). Thus, the ability of the active avoidance test to detect antipsychotic activity does not seem to be solely limited to the detection of drugs with

direct dopamine D2 receptor blocking properties. This certainly increases the value of this test as a screening tool in further development of new antipsychotic drugs, since many current development strategies, in order to minimize side effects and improve therapeutic efficacy, aim at moving away from molecules with mainly strong dopamine D2 receptor blocking properties.

Alternative Use of the Active Avoidance Test

The active avoidance test is primarily a test for detecting antipsychotic activity, that is, the ability of tested compounds to counteract psychotic symptoms in patients. However, since there is an element of training and learning (acquisition) associated with this test, there have been attempts to investigate if the test may be used also as a model for the detection of compounds that will enhance learning (effects on acquisition) or memory (effects on retention). Such attempts have overall not produced any consistent data. In fact, drugs that normally would impair memory (such as for example, drugs blocking brain neural transmission of acetylcholine) do not suppress avoidance behavior. Furthermore, the administration of a dopamine D2 receptor blocking antipsychotic to the animals during the training/acquisition phase does not impair the final outcome of avoidance performance in the absence of drug. This would suggest that suppressive effects on avoidance performance are not related to the impairment of memory, but rather to a temporary attenuation of the conditioned reflex, or urge, to hurry over to the other side in order to avoid getting a footshock. Indeed, gross observations of the behavior in animals given an antipsychotic drug strongly indicate that upon presentation of the CS, these animals still remember exactly what they are supposed to do; they just do not care enough to move within the time frame. Another way of explaining this phenomenon, although somewhat speculative, could be that the reason why active avoidance does not seem to work as a memory test, is because the acquisition and retention performance of active avoidance seem to primarily involve the brain subcortical mesolimbic system in general considered to be mediating behavior associated with basic reward and survival factors (i.e., survival reflexes), rather than recruiting higher order brain structures, such as for example, the prefrontal cortex, that are involved in memory processes of higher order events (Wadenberg et al. ▸8).

Advantages and Limitations of the Active Avoidance Test

The active avoidance test has proven to be a unique and very useful screening test for the detection of drugs with antipsychotic activity with high predictive validity as well as excellent reliability. However, individuals suffering from schizophrenia do not only present with psychotic symptoms, but also

have features of social withdrawal and cognitive impairment. These symptoms have a crucial impact on the quality of life for these individuals, and unfortunately, many of the currently used antipsychotics do not adequately improve these symptoms. Therefore, novel compounds showing antipsychotic-like effects in the active avoidance test, need to be tested also in an animal model of cognition as a complementary investigation of their potential cognitive enhancing activity compared with currently used antipsychotics. A major improvement in the field would be the development of an animal behavioral screening test that identifies both antipsychotic and cognitive enhancing activity of tested drugs.

Cross-References

▸Animal Models for Psychiatric States

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Aggressive Behavior: Clinical Aspects

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Synonyms

Aggressiveness
Aggressive behavior
Agonistic behavior
Impulsive aggression
Violence

Definition

Behavior by an individual directed at another person or object in which either verbal force or physical force is used to injure, coerce, or express anger.

Role of Pharmacotherapy

Types of Clinical Aggression

Human aggression constitutes a multidetermined act that results in physical or verbal injury to self, others, or objects. It appears in several forms and may be defensive, premeditated (e.g., predatory), or impulsive (e.g., nonpremeditated) in nature. Defensive aggression is generally seen as dictated by particular external realities and within the normal range of human behavior. Premeditated and impulsive aggressive behaviors are commonly viewed as pathological. Specific acts of aggression may be situational, but

the tendency to behave aggressively represents a behavioral trait. While the frequency of aggressive acts tends to decrease with advancing age, numerous studies document that the trait of aggressiveness begins early in life and continues through adulthood. Both impulsive and premeditated aggression represents the potential for significant physical and psychological harm to the individual, to those subjected to the effects and to society in general. However, a converging pattern of empirical data from a variety of studies consistently links *impulsive*, but not premeditated, aggression to biological, environmental, and pharmacological or psychological treatment response factors.

One guiding principle to the consideration of human aggression is that biological and psychological factors contribute significantly to this behavior. Biological factors contribute to aggressive behavior through reduced inhibitory, and/or increased facilitatory, neuronal inputs to behavior. Research in this area has found utmost support for the role of inhibitory behavioral inputs modulated by brain serotonin (5-HT) function. The role of various neurotransmitter systems in increasing facilitatory input for aggressive behavior has received less attention and, in contrast to 5-HT, the results have been somewhat inconsistent. On the other hand, psychotherapy outcome research has successfully focused attention in this general area, vis-a-vis the relationship between the impulsive aggressive individual and his/her external/internal environment as facilitatory in generating impulsive aggressive behavior. Here, the focus is on the hypothesis that vulnerable individuals manifest impulsive aggressive behavior in response to external/internal stimuli perceived as "provocative" or "aversive" in nature which lead to variable states of anger that drive susceptible individuals (e.g., individuals with reduced central 5-HT function) to exceed their "threshold" for effective behavioral inhibition so that an impulsive aggressive outburst is initiated. If so, treatment aimed at increasing central (5-HT mediated) behavioral inhibitory tone and reducing states of high anger (i.e., negative emotionality) should be an effective strategy in treating impulsive aggressive behavior in human subjects. To date, research has shown the potential efficacy of (1) pharmacological approaches to reducing impulsive aggressive outbursts and, (2) psychological approaches to reducing states of acute (and chronic) anger. To date, however, neither approach has been combined or compared in the same study.

Impulsive Aggression Expressed as a Dimension

Behavioral Genetics of Impulsive Aggression

Data from twin, adoption, and family studies suggest genetic influence on aggression. Heritability estimates for measures of aggression are moderately

substantial in adults ranging from 44% to 72% and a recent meta-analysis confirmed the presence of a substantial genetic influence for aggression. Heritability estimates were most pronounced for aggression measures reflecting anger and hostility, or anger, impulsiveness, and irritability. It is noteworthy that these same phenomena are associated with the clinical profile of intermittent explosive disorder (IED).

Psychosocial/Environmental Correlates of Impulsive Aggression

The most important psychosocial factors involved in the development of aggression appear to be low socioeconomic status, ineffective parenting style, as well as physical punishment in childhood and exposure to aggression within and outside of the family. Notably, harsh discipline and child abuse (regardless of SES status) have been found to predict the development of *impulsive*, but not nonimpulsive, aggressive behavior in children. In one study, 41% of children abused in the first 5 years of their life became *impulsively* aggressive later in life, compared with 15% of nonabused children; in contrast, none of the nonimpulsively aggressive subjects had a history of child abuse.

Neurochemical Correlates of Impulsive Aggression

Among all of the biological factors potentially involved in aggression, the most studied factors relate to brain neurochemistry, specifically monoamines such as serotonin (5-HT) and other centrally acting neurotransmitters (Brown et al. ▸1; Coccaro and Siever ▸2; Coccaro et al. ▸3). Evidence of a role of brain 5-HT in human aggression is especially strong and points to an inverse relationship between brain 5-HT activity and aggression in animal models, nonhuman primates, and humans. In human studies, various measures reflecting central (as well as peripheral) 5-HT function have been shown to correlate inversely with life history, questionnaire, and laboratory measures of aggression. Most importantly, the type of aggression associated with reduced central 5-HT function appears to be *impulsive*, rather than nonimpulsive aggression (Linnoila et al. ▸8). In human studies, there are selective cases where the relationship between 5-HT and aggression is positive in direction or does not exist at all. This may be due to the presence of other factors (e.g., diagnostic group; drug dependence; developmental stage) which may involve differential contributions from other neurotransmitter systems that also influence the tendency to react aggressively in social contexts. Limited evidence also supports a role for Non-5-HT brain systems and modulators in impulsive aggression. These findings suggest a permissive role for ▸dopamine, norepinephrine, vasopressin, testosterone, and an inhibitory interaction between neuronal nitric oxide synthase and testosterone in rodents.

Functional Neuroanatomy of Aggression-Related Disorders in Humans

While IED is the only DSM-IV disorder (see later) for which aggression is the cardinal symptom, both borderline personality disorder (BPD) and antisocial personality disorder (AsPD) share a number of attributes associated with aggression as a dimension. At their most basic level, all three disorders are associated with increased anger and irritability as well as self- and other-directed aggression. All three diagnostic groups demonstrate a number of the deficits associated with the orbital medial prefrontal cortex (OMPFC)-amygdala tract including deficiencies of executive functions and socioemotional information processing. For IED, a series of PET studies on "impulsive aggressive" patients with both IED and BPD fail to parallel the increase in OMPFC metabolism by normal controls in response to acute administration of serotonin agonists, suggesting an important reduction in OMPFC function in impulsive aggressive individuals (New et al. ▸10). Notably, however, chronic administration of a serotonin agonist over 12 weeks can both increase OMPFC metabolism and reduce impulsive aggressive behaviors. A study of temporal lobe epilepsy patients with and without IED, found that a subgroup of 20% of the IED patients (BPD status not assessed) had "severe" amygdala atrophy. In contrast to these studies, the only available imaging data from subjects with IED, demonstrate that IED subjects (even those without BPD or AsPD) have augmented Amygdala (AMYG), and reduced OMPFC, fMRI blood oxygenated level dependent (BOLD) signal activation to angery faces (Coccaro et al. ▸5). In contrast to IED, there is a larger imaging literature among patients with BPD and AsPD. Structural MRI studies show only weak support for the existence of reduced frontal volumes for either disorder with equally equivocal support for morphological changes in the amygdala. In contrast, PET and fMRI studies have produced a fairly consistent pattern of altered corticolimbic activation for both disorders. Three PET studies have reported reduced metabolism in the frontal (e.g., OMPFC) cortex in BPD subjects. Both BPD and AsPD populations show decreased OMPFC activation during emotional information processing (e.g., trauma scripts, a conditioned aversive stimulus) compared to control populations. Psychopaths also evidence less activation to abstract words in the right lateral frontal cortex. Both groups show increased amygdala activation to emotional stimuli; BPD subjects display enhanced amygdala activation to unpleasant pictures, as well as fearful and neutral words (viewed as negative by BPD subjects). While psychopaths showed increased amygdala activation when passively viewing negatively valenced pictures, amygdala activation for psychopaths may be attenuated/eliminated during emotional learning/conditioning tasks.

Recurrent, Problematic, Impulsive Aggressive Behavior as a Target for Study and Intervention: Intermittent Explosive Disorder

Although the term IED has only been in the DSM since the third edition (1980), the "construct" of a "disorder of impulsive aggression" has been in the DSM since its inception in 1956. Currently, it describes individuals with recurrent, problematic episodes of aggression not accounted for by other medical or psychiatric factors (Coccaro et al. ▸1). While DSM-IV does not specifically refer to the aggression in IED as impulsive in nature, premeditated aggression is typically a characteristic seen in antisocial personality disorder.

Clinical Description

Aggressive outbursts in IED have a rapid onset, often without a recognizable prodromal period. Episodes are typically short-lived (less than 30 min) and involve verbal assault, destructive and nondestructive property assault, or physical assault. Aggressive outbursts most commonly occur in response to a minor provocation by a close intimate or associate, and IED subjects may have less severe episodes of verbal and nondestructive property assault in between more severe assaultive/destructive episodes. The episodes are associated with substantial distress, impairment in social functioning, occupational difficulty, and legal or financial problems.

Epidemiology

In the largest epidemiological study to date, the lifetime prevalence of IED by "Narrow" DSM-IV criteria is estimated at 5.4% with 1-year prevalence estimated at 2.7% (Kessler et al. ▸1).

Age of Onset and Demographics

IED appears as early as childhood and peaks in mid-adolescence, with a mean age of onset in three separate studies ranging from 13.5 to 18.3 years. The average duration of symptomatic IED ranges from 12 to 20 years to the whole lifetime. While initially thought to be more common in males, recent data suggest the gender difference in prevalence of IED may be closer to 1:1. Sociodemographic variables (e.g., sex, age, race, education, marital and occupational status, family income) do not appear to differ meaningfully as a function of IED status.

Laboratory Studies

To date, published data have reported IED subjects as having altered serotonin function compared with non-IED subjects or healthy controls. Other studies demonstrate a reduction in prolactin responses to fenfluramine challenge, in the numbers of platelet 5-HT transporters in IED subjects

compared with non-IED subjects. Two FDG PET studies report low FDG utilization after d,l-fenfluramine challenge in frontal areas of the brain and low FDG utilization after m-CPP challenge in the anterior cingulate in IED subjects compared with healthy controls. A ligand binding study of the 5-HT transporter also reports reduced low 5-HT transporter availability in the anterior cingulate in IED subjects versus healthy controls. Finally, fMRI study demonstrates increased activation of AMYG, and reduced activation of OMPFC, to angry faces, in IED subjects compared with healthy controls.

Family Study

Family history study of IED subjects demonstrates a significantly elevated morbid risk for IED in relatives of IED, compared with healthy controls, probands (0.26 vs. 0.08, $p < 0.01$). Elevation in morbid risk for IED was not due to the presence of comorbid conditions among IED probands (e.g., history of suicide attempt, major depression, alcoholism, drug use disorder, etc.) and not due to elevations in morbid risk of other non-IED disorders in relatives (e.g., major depression, alcoholism, drug use disorders, anxiety disorder, and any other disorder).

Treatment of Impulsive Aggression and IED

Impulsive Aggression

Several psychopharmacologic agents appear to have effects on impulsive aggression. Classes of agents shown to have "antiaggressive" effects in double-blind, placebo-controlled trials of individuals with "primary" aggression (i.e., not secondary to psychosis, severe mood disorder, or organic brain syndromes) include mood stabilizers (e.g., lithium), 5-HT uptake inhibitors (e.g., fluoxetine) and, anticonvulsants (e.g., diphenylhydantoin, carbamazepine). While norepinephrine beta-blockers (e.g., ▸propranolol, nadolol) have also been shown to reduce aggression, these agents have exclusively been tested in patient populations with "secondary" aggression (e.g., mental retardation, organic brain syndromes, etc.). Classes of agents which may have also "pro-aggressive" effects under some conditions include tricyclic antidepressants (e.g., amitriptyline), benzodiazepines, and stimulant and hallucinatory drugs of abuse (e.g., amphetamines, cocaine, ▸phencyclidine). Emerging evidence of differential psychopharmacology is of critical importance, and findings from the literature of double-blind, placebo-controlled, clinical trials suggest that antiaggressive efficacy is specific to *impulsive*, rather than nonimpulsive, aggression.

Intermittent Explosive Disorder: Effect of Psychopharmacologic Intervention

Fluoxetine demonstrates clear antiaggressive efficacy for reducing impulsive aggressive behavior in IED subjects compared with placebo (Coccaro et al. ▸6). Fluoxetine's antiaggressive effect is most clearly seen on verbal aggression and aggression against objects. Despite this effect, somewhat less than 50% of IED subjects treated with fluoxetine achieve remission. Gains made with fluoxetine typically dissipate within 1 month after discontinuation but can be achieved again when the drug is reinstituted. Notably, fluoxetine has not been shown to increase aggression in IED subjects in placebo-controlled trials. Another placebo-controlled study of IED involving divalporex reported a favorable effect of this agent on overt aggression but only in IED subjects with comorbid cluster B personality disorder.

Intermittent Explosive Disorder: Effect of Psychosocial Intervention

While there are very few studies on the psychosocial treatment of impulsive aggression in adults, the efficacy of treatments that address the related constructs of anger dyscontrol and/or interpersonal aggression have been evaluated and suggest that relaxation training, interpersonal skill training, cognitive therapy, and multicomponent treatments all have moderate to large effects in the treatment of anger, and that the anger-reducing effects of anger treatment remain at follow-up. Of the different approaches for treating individuals with anger and aggression problems, cognitive restructuring, interpersonal skills training, multicomponent treatments, and relaxation skills had the strongest influence on aggression with effect sizes (Cohen's d) for the four types of treatment ranging from 1.06 to 1.87. Recently, a well-controlled study of cognitive behavior therapy in IED focusing on cognitive restructuring, relaxation and coping skills training has been published, demonstrating significant reduction in impulsive aggressive behavior and in hostile automatic thoughts (McCloskey et al. ▸9). The antiaggressive response in this study was similar to that seen with fluoxetine, suggesting the possibility that the two interventions, together, may be very effective in treating the impulsive aggression seen in individuals with IED.

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Akathisia

Definition

A syndrome of increased motor activity and/or subjective sense of desire for motor activity believed to be due to functional irregularities in the extrapyramidal motor system in the brain. Most blatantly, akathisia may involve fidgeting, inability to remain seated, shuffling gait, shortened stride, cogwheel rigidity, reduced accessory movements such as arm-swing while walking or gesturing, and pacing. It may include more subtle phenomena such as wandering (with attendant boundary issues) and excessive talking (which the patient may be aware of, but unable properly to control). Aki-

nesia can also affect small muscle groups, such as those of the face and/or larynx, leading to a reduced amount and range of facial expression and/or monotonous voice tone. Subjectively, akathisia is frequently experienced as an unpleasant, dysphoric state.

Akinesia

Synonyms
Pseudo-parkinsonism

Definition
Reduced spontaneous movements.

Alogia

Definition
Poverty of speech, as in schizophrenia.

Aminergic Hypothesis for Schizophrenia

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Definition
An explanation for the pathophysiology of schizophrenia and mechanism of action of antipsychotic drugs with a special focus on aminergic (dopamine, serotonin, and noradrenaline) neural systems.

Role of Pharmacotherapy
Schizophrenia is characterized by a variety of symptoms, including hallucination, delusion, and psychomotor excitement. A dopamine receptor antagonist, ▸chlorpromazine, was introduced in the treatment of this illness in 1952 and has shown its effectiveness, which has made the dopaminergic system a primary target of research on the pathogenesis of schizophrenia as well as potential mechanisms of antipsychotic action of this type of drugs.

This has led to the prototype of the dopaminergic hypothesis for schizophrenia where the increase and decrease in the dopaminergic neural transmission is attributed to its symptoms and treatment effects of ▸antipsychotic drugs, respectively. Although this hypothesis has been revisited and further developed, the dopaminergic system cannot fully account for the mechanisms underlying this illness. Recently, other neural systems such as glutamatergic and cholinergic systems have also come to the front line of this line of research.

▸Dopamine was the first target of research on schizophrenia, and is still considered to play a primary role in the pathogenesis of this illness and mechanisms of actions of antipsychotic drugs. The hypothesis that explains the involvement of the dopaminergic system in this illness (the dopamine hypothesis) has been supported by a vast amount of both animal and human studies and further occasionally updated with the accumulation of relevant new clinical and basic data. The first version of the dopamine hypothesis focused on the dopaminergic receptors where psychosis was considered to be due to excessive transmission at dopaminergic receptors and diminished by blocking these receptors. The most widely accepted support for this hypothesis is the fact that dopamine antagonist antipsychotic drugs can relieve psychotic symptoms. The first antipsychotic drug, chlorpromazine, was introduced in the treatment of schizophrenia in 1952. As this type of medication had been found to have a dopamine receptor blocking property, the dopaminergic system came to the forefront of scientific inquiry. While blockade of dopamine receptors had already been thought to be associated with therapeutic effects of antipsychotic medications in the 1960s and 1970s, Seeman et al. first systematically demonstrated that the degree of dopamine receptor antagonism by antipsychotics was closely associated with their antipsychotic efficacy in 1976 (Seeman et al. ▸10). This relationship is still valid after ▸second-generation antipsychotics have become available, although ▸clozapine seems exceptional, as we discuss next. Another frequently referred support for this hypothesis is the presence of psychotic symptoms associated with the administration of amphetamine. Both animal and human studies have demonstrated the increase of endogenous dopamine levels, following amphetamine administration, and shown that amphetamine-induced psychotic symptoms resemble schizophrenic symptoms. Furthermore, these amphetamine-induced psychotic symptoms are reversible with the use of dopamine antagonist antipsychotic drugs. In addition, psychotic symptoms caused by amphetamine administration in drug-free schizophrenia patients were found to be associated with exaggerated stimulation of dopaminergic transmission, compared to those who did not

present those symptoms following its administration (Laruelle et al. ▸7) – lending further support to this model.

In 1980, Crow proposed a hypothesis where schizophrenia could be grouped into two separate conditions: the type I syndrome characterized by positive symptoms, including delusion, hallucinations, and thought disorder, and type II syndrome characterized by negative symptoms, including affective flattering and poverty of speech (Crow ▸2). In this theory, the type I syndrome was considered to be associated with high dopaminergic activity and reversible with antipsychotic treatment while negative schizophrenic symptoms were thought to be caused by deficiency in the dopaminergic function and involve a component of irreversibility. This hypothesis tried to comprehensively link potential pathogenesis and symptomatology of schizophrenia to the dopaminergic system. Although this proposal has often been criticized later due to its simple dichotomization and a lack of sufficient convincing biological support, its impacts on further investigations have still been tremendous. In 1991, Davis et al. published a landmark review and proposed the co-occurrence of high and low dopamine activities in schizophrenia to the concurrent presence of positive and negative symptoms (referred to as the dopamine hypothesis, Version II) (Davis et al. ▸3). Evidence, particularly from intracellular recording studies in animals and plasma homovanillic acid (HVA) measurements, suggests that antipsychotics exert their effects by reducing dopamine activity in mesolimbic dopamine neurons. Postmortem studies have shown high dopamine and HVA concentrations in various subcortical brain regions and greater dopamine receptor densities in patients with schizophrenia, compared to healthy people. On the other hand, they attributed the negative/deficit symptom complex of schizophrenia to low dopamine activity in the prefrontal cortex, which is now known as "hypofrontality". Davis et al. hypothesized that abnormally low prefrontal dopamine activity caused deficit symptoms in schizophrenia, while excessive dopamine activity in mesolimbic dopamine neurons resulted in positive symptoms.

With further accumulation of basic and clinical data on the function of the dopaminergic system, psychopathology of schizophrenia, and potential mechanisms underlying treatment effects of antipsychotics, Kapur reviewed those findings (Kapur ▸6) and linked the neurobiology (brain), the phenomenological experience (mind), and pharmacological aspects of psychosis in schizophrenia into a unitary framework. A central role of dopamine is to mediate the "salience" of environmental events and internal representations. It is proposed that a dysregulated, hyperdopaminergic state at a "brain" level of description and analysis leads to an aberrant assignment of salience to the elements of one's experience at a "mind" level. This would

result in delusions as a clinical manifestation as patients make a cognitive effort to make sense of these aberrantly salient experiences. On the other hand, ▸hallucinations reflect a direct experience of the aberrant salience of internal representations. Antipsychotic drugs are expected to dampen the salience of these abnormal experiences and by doing so permit the resolution of symptoms, where the antipsychotics are thought not to erase the symptoms but to provide the platform for a process of psychological resolution. Therefore, if antipsychotic treatment is stopped, the dysregulated neurochemistry returns, the dormant ideas and experiences become reinvested with aberrant salience, resulting in a relapse. Although this hypothesis does not explain the mechanisms of negative symptoms of schizophrenia, current ideas regarding the neurobiology and phenomenology of psychosis and schizophrenia, the role of dopamine, and the mechanism of action of antipsychotic medication are integrated.

In its latest iteration, Howes et al. proposed the updated version of the dopamine hypothesis (Version III), where multiple factors, including stress and trauma, drug use, pregnancy and obstetric complications, and genes, interact to result in the increased presynaptic striatal dopaminergic function in schizophrenia (Howes and Kapur ▸5). This striatal dopaminergic dysregulation is considered the final common pathway of the pathogenesis of this illness, in this theory. This hypothesis suggests that current treatments act downstream of the critical neurotransmitter abnormality and emphasized the need of future drug development with a focus on the upstream factors that converge on the dopaminergic funnel point.

However, pathogenesis of schizophrenia and the resolution of its symptoms with antipsychotics are not expected to be solely related to the effects in the dopaminergic system. Superior clinical effects of clozapine despite its low dopamine D2 receptor blocking propensity are one example of the limitations of the dopamine hypothesis. There are several others: many patients do not respond despite adequate dopamine blockade, some respond with rather low D2 blockade, and many relapse despite adequate D2 blockade. So, clearly the genesis of psychosis and its response depends on more than just dopamine. But, precisely what is beyond dopamine – has been harder to confirm. The involvement of other neural systems such as the glutamatergic, cholinergic, and serotonergic systems has been proposed.

Several lines of evidence suggest that the glutamatergic neural system is also involved in the pathogenesis of schizophrenia (Bubenikova-Valesova et al. ▸1). Glutamate acts through several types of receptors, of which the ionotropic glutamate N-methyl-D-aspartate (NMDA) receptor has been considered to be closely associated with schizophrenia (i.e. the glutamate hypothesis of schizophrenia). The most prominent support for this hy-

pothesis is the acute psychomimetic effects of noncompetitive antagonists of glutamate NMDA receptors, such as ▸phencyclidine and ketamine. These drugs have been shown to change both human and animal behavior and induce schizophrenia-like manifestations. For example, ketamine has been demonstrated to cause a variety of schizophrenia-like symptoms in healthy people, including positive symptoms (e.g., illusions, thought disorder, and delusions), negative symptoms (e.g., blunted emotional responses, emotional detachment, and psychomotor retardation), and cognitive symptoms, in particular impairments on tests of frontal cortical function (e.g., increased distractibility and reduced verbal fluency). In patients with schizophrenia, ketamine causes auditory or visual hallucinations while antipsychotics significantly reduce the ketamine-induced increase in positive symptoms. This hypothesis is also in line with the neurodevelopmental model of schizophrenia. Susceptibility to the psychotomimetic effects of ketamine is minimal or absent in children and becomes maximal in early adulthood, which is consistent with the fact that many schizophrenia patients experience their first episode until their 20s. Increased cellular destruction by apoptosis or changes in the function of NMDA receptors in the early development of the central nervous system are expected to be decisive for the subsequent development of psychosis, which in turn would be expected to finally manifest in their early adulthood. However, although pharmacological intervention to the NMDA receptors, using their antagonists, may lead to the development of novel therapeutic agents for schizophrenia in theory, no agent has been available until now.

The available evidence also suggests an important role for the muscarinic cholinergic system in the pathophysiology of schizophrenia (Raedler et al. ▸8; Scarr and Dean ▸9). Acetylcholine is synthesized in neurons from acetyl-CoA and choline in a reaction catalyzed by the enzyme choline acetyltransferase. There are two families of acetylcholine receptors: muscarinic receptors and nicotinic receptors. Muscarinic cholinergic neurotransmission has been shown to play a significant role in various cognitive functions, including learning and memory, which has lead to a hypothesis that these receptors are involved in cognitive impairment in schizophrenia (the cholinergic hypothesis of schizophrenia). Postmortem and in vivo brain imaging studies have consistently shown a significant decrease of muscarinic M1 receptor density, and this decrease is seen in patients with schizophrenia but not those with bipolar disorder or major depression. Thus, these changes are expected to be disease-specific and considered to be associated with deficits in the cognitive function in schizophrenia. Pharmacological studies of the muscarinic system in schizophrenia have indicated that targeting muscarinic M1 receptor might be an effective strategy to ameliorate the

cognitive impairment in schizophrenia. Although stimulating cholinergic neurotransmission, using cholinesterase inhibitors, has not yielded promising therapeutic effects on cognitive function in schizophrenia, muscarinic M1 agonists have been shown to improve cognitive function. For example, N-desmethylclozapine, an active metabolite of ▸clozapine, is a potent M1 agonist and has gathered attention as a new pharmacological agent for the treatment of schizophrenia although the data are still preliminary. Thus, the currently available evidence suggests that deficits in muscarinic M1 neurotransmission in brain are associated with cognitive impairments in schizophrenia. Although there is no clinically available muscarinic M1 agonist as a cognitive enhancer for the treatment of schizophrenia, the preliminary data indicate the potential benefits of targeting these receptors to improve cognitive function in patients with this illness.

The potential involvement of the serotonergic system in the pathogenesis of schizophrenia was first proposed earlier than the dopamine hypothesis. Based on a phenomenological similarity between psychosis-like effects of lysergic acid diethylamide (LSD) and symptoms of schizophrenia, it was proposed in the mid 1950s that the abnormal neural transmission in the serotonergic system may be responsible for psychotic symptoms in schizophrenia (referred to as the serotonergic hypothesis of schizophrenia). A subsequent series of human and animal studies have confirmed that 5-HT2A-receptor agonists such as LSD and psilocybin have effects that mimic schizophrenia-like symptoms (Geyer and Vollenweider ▸4). These findings seem to support that psychopharmacological intervention in the serotonergic neural system may be promising for drug development, which is not the case in reality. Antipsychotic drugs such as clozapine and chlorpromazine had significantly higher affinity for 5-HT2 than for D2 receptors. However, as described earlier, the degree of dopamine receptor antagonism (rather than their 5-HT2 antagonism) by these antipsychotics has been shown to be more closely associated with their antipsychotic efficacy, suggesting that 5-HT2 blockade is not the principal mechanism of their antipsychotic action. Consistent with this contention, clinical trials have failed to provide robust antipsychotic effects of selective antagonists at 5-HT2A receptors until now. Some atypical antipsychotics, including ▸risperidone, have been suggested to have a safer side effect profile in motor function, which may be due to their 5-HT2A antagonistic property. Although antagonism at 5-HT2A when added to D2 antagonism may contribute to the safe profile of those newer drugs, targeting solely serotonergic neural transmission is unlikely to provide antipsychotic effects for the treatment of schizophrenia.

In summary, while the current data suggest the involvement of several aminergic neural systems in the pathophysiology of schizophrenia and mechanisms of actions of antipsychotics drugs, the dopaminergic system is still considered to play a principal role. In fact, there is no effective antipsychotic that does not have an effect on the dopamine system. On the other hand, nonpsychotic symptoms, especially negative symptoms and cognitive impairment, may be reversed with the use of drugs working on nondopaminergic neural systems such as the glutamatergic and cholinergic system. Given that manipulating the dopaminergic system is effective, but not always perfect for the treatment of schizophrenia, further psychopharmacological research on other neural systems would also be needed.

Cross-References

▸Animal Models for Psychiatric States
▸Atypical Antipsychotic Drugs
▸Dopamine
▸First-Generation Antipsychotics
▸Hallucinations
▸Schizophrenia
▸Second and Third Generation Antipsychotics

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Amisulpride

Definition

Amisulpride is a benzamide derivative and is a second-generation antipsychotic with high affinity for D2 and D3 receptors. Its pharmacology is unusual in that at low doses, amisulpride preferentially blocks presynaptic D2 receptors, while at high dose it acts as an antagonist at postsynaptic D2 receptors. Amisulpride is used for the treatment of positive and negative symptoms of ▸schizophrenia, as well as the management of dysthymia. Its therapeutic and safety profile is similar to that of the atypical antipsychotic ▸risperidone, but amisulpride is associated with less weight gain and endocrine disturbance.

Angel Dust

Cross-References

▸Antipsychotic Drugs
▸Ketamine
▸Phencyclidine

Animal Models for Psychiatric States

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Synonyms

Animal models of psychopathology
Behavioral models of psychopathology
Simulations of psychopathology

Definition

Animal models of psychiatric states are procedures applied to laboratory animals that engender behavioral changes which are intended to be homologous to aspects of psychiatric disorders, and can therefore be used as experimental tools to further the understanding of human psychopathology.

Principles and Role in Psychopharmacology

Basic Concepts

The concept of modeling psychopathology in animals is as old as the use of animals in psychological investigations: its roots may be found in the work of Pavlov, Watson, and even earlier. However, for many years, practical attempts to devise animal models were sporadic, ad hoc, and unconvincing. As a result, animal models of psychiatric states were until recently viewed with justified suspicion. Over the last 20–30 years, this situation has changed, with the recognition that animal models can provide a means of investigating the neurobiological mechanisms underlying psychopathology. Indeed, given the limitations of the investigational techniques currently available for use in human subjects, animal models represent the only means of asking many important questions. Animal models can also be of great value in the process of psychotropic drug development, and again, frequently represent the only viable method of predicting novel therapeutic actions. The recent development and acceptance of animal models may thus be seen as an adjunct to the concurrent growth and maturation of psychopharmacology and biological psychiatry, where they serve as indispensable tools for translational research.

The definition of animal models of psychiatric states presented above includes a number of features:

1. The *procedures* used to generate models are many and varied. Broadly, they involve environmental manipulations (e.g., exposure to social or

physical stressors, or training regimes), and/or alteration of the internal environment (e.g., by brain lesions or administration of psychotropic drugs), and/or identification of vulnerable individuals (by selective breeding or genomic methods). Some examples of each of these procedures are shown in Table ▸1.

Animal Models for Psychiatric States. Table 1. Some examples of the procedures used to construct animal models of psychiatric states.

General procedure	Specific example	Primary behavioral end point	Condition modeled
Manipulation of the external environment			
Social stress	Social conflict	Loser in competition for food source	Anxiety[▸a]
	Isolation rearing	Impairment of prepulse inhibition	Schizophrenia[▸b]
Physical stress	Uncontrollable footshock	Impairment of avoidance learning ("learned helplessness")	Depression [▸c]
	Chronic mild stress	Decreased response to rewards	Depression [▸c]
Training [▸i]	Operant responding for intravenous drug administration[▸k]	Drug self-administration [▸k]	Drug addiction[▸d]
	Punished operant responding	Suppression of responding by a signal paired with punishment[▸j]	Anxiety[▸a]
Manipulation of the internal environment			
Drug administration	▸Phencyclidine	Stereotyped behavior and decreased social contact[▸m]	Schizophrenia[▸b]
	Scopolamine	Impairment of ability to remember information across short time delays [▸l]	Dementia[▸e]

(Continued)

General procedure	Specific example	Primary behavioral end point	Condition modeled
Brain lesion	Olfactory bulbectomy	Locomotor hyperactivity	Depression [▸c]
	Neonatal hippocampal lesion	Locomotor hyperactivity and hyper-responsiveness to stress	Schizophrenia[▸b]
Identification of vulnerable individuals			
Selective breeding	Flinders sensitive line (FSL) rat	Increased immobility in the forced swim test[▸f]	Depression [▸c]
	High saccharin–consuming (HiS) rat	Self-administration of cocaine and heroin[▸k]	Drug addiction[▸d]
Genomic manipulations[▸h]	Transgenic rat overexpressing amyloid precursor protein	Impairment of spatial learning[▸n]	Dementia[▸e]
	5HT 1A receptor knockout mouse	Avoidance of open spaces[▸g]	Anxiety[▸a]

The models listed in this table are chosen in order to illustrate the breadth of animal models in current use. There is no implication that these are the "best" or most valid models available

[a] Anxiety: Animal Models
[b] Schizophrenia: Animal Models
[c] Depression: Animal Models
[d] Addictive Disorder: Animal Models
[e] Rodent Models of Cognition
[f] Behavioral Despair
[g] Elevated Plus-Maze; Open Field Test
[h] Genetically Modified Animals
[i] Operant Behavior in Animals

[j] Pavlovian Fear Conditioning; Punishment Procedures
[k] Self-Administration of Drugs
[l] Short-Term and Working Memory in Animals
[m] Social Recognition and Social Learning
[n] Spatial Learning in Animals

2. While in principle any animal species could be used, in practice the scope of modeling is restricted to *laboratory animals*. The most extensively used species has traditionally been the rat, but mouse models are being increasingly developed in order to capitalize on the availability of genetically modified strains. (Genetically modified animals) Other species used occasionally include guinea pigs, marmosets, and chicks.
3. Some earlier definitions of animal models described them as analogous to psychiatric disorders. The present definition emphasizes that models aim to be *homologous*: that is, to simulate essentially the same process across species. This issue is discussed further below.
4. An animal model of a psychiatric disorder includes a behavioral end point, which represents a model of a process that is thought to be important in the disorder. The scope of models is typically limited: they aim to simulate specific *aspects* rather than the entirety of the disorder, though it may be found subsequently that further aspects of the disorder are also present. Table ▸1 lists the primary behavioral end points that were the focus of the original publications on each model, but in almost every case, a variety of other behavioral changes have also been described.
5. The definition also emphasizes the purpose of animal models of psychopathology: to provide a means of studying aspects of mental disorders. Animal models are *experimental tools*, and they are developed for specific investigational purposes. Initially, the primary aim was to elucidate psychological processes, but models are now used largely to address neurobiological issues. The specific issues most commonly addressed include: mechanisms of action of psychotherapeutic drugs, the neurotransmitter, neuroreceptor, and intracellular changes underlying psychiatric states, the neuroanatomical basis of psychiatric states, and increasingly, questions about the role of specific genes.

This article discusses some general issues concerning animal models of psychiatric states; models of specific psychiatric states are discussed elsewhere. Animal models; Anxiety: Animal Models; Autism: Animal Models; Dementias: Animal Models; Depression: Animal Models; Eating Disorder: Animal Models; Primate Models of Cognition; Rodent Models of Cognition; Schizophrenia: Animal Models. The references at the end of this article

provide further reviews of this general area, from a variety of different perspectives.

Fitness for Purpose

Because models are built to be used, they have to be viewed in relation to the broader objectives of a research program. Behavioral models are used in psychopharmacology for two distinct purposes: as simulations within which to study aspects of psychiatric states, and as screening tests for the development of new treatments. Screening tests are subject to logistical considerations: for example, the test should be completed in the shortest possible time, and ideally will respond to acute drug treatment. However, in a model of a psychiatric state, these same features may be counter-indicated. For example, antidepressant drugs are clinically ineffective if administered acutely and largely inert if administered to nondepressed people: therefore, a model of clinical antidepressant action should involve chronic drug treatment, administered within a context of abnormal behavior rather than to "normal" animals. (Antidepressants) Thus, a particular time course of antidepressant action and a particular level of behavioral sophistication may be desirable or undesirable features, depending upon the purpose for which a procedure is being used.

Conclusions arising from the use of a model are essentially hypotheses, which must eventually be tested against the clinical condition being modeled. The more valid a model, the more likely it is that insights derived from it will hold true for the clinical condition. Therefore, an assessment of the validity of a model provides an indication of the degree of confidence that we can place in the hypotheses arising from its use. Assessment of validity is not a yes/no judgment, but rather an evaluation of strengths and weaknesses and areas of uncertainty.

The systematic validation of an animal model is no different in principle from that of any other psychological device, such as a psychometric test or a psychiatric diagnosis, and the same general approaches to validation are applicable. Several systems of evaluation have been proposed, which have the common feature that models are assessed on two or more independent dimensions. One widely used method, described below in more detail, employs the three dimensions of predictive, face, and construct validity: predictive validity means that performance in the test predicts performance in the condition being modeled (and vice versa); face validity means that there are phenomenological similarities between the two; and construct validity means that the model has a sound theoretical rationale.

Some reviewers have advocated the primacy of one of these three dimensions, and each has its advocates. In principle, construct validity should be considered as the most fundamental dimension. In practice, however, the

construct validity of animal models of psychopathology is difficult to determine, and therefore a balanced approach is needed, in which a view of the validity of a model is formed only after considering all three sources of evidence. In all three areas, discriminant validity is a further consideration: that is, the extent to which the evidence points to a particular disorder, as distinct from a different or a nonspecific psychiatric disorder. The three sets of validation criteria provide a convenient framework for organizing large volumes of data and ensuring that when different models are compared, like is compared with like. The major issues described below are summarized in Table ▸2.

Animal Models for Psychiatric States. Table 2. Issues to consider in assessing the validity of animal models.

Predictive validity	Specificity: No false positives
	Sensitivity: No false negatives
	Relative potencies and appropriate dose ranges
	How firmly established are the clinical data on effective and ineffective treatments?
Face validity	Extent of correspondence vis-à-vis symptoms and neurobiological features
	Specificity of symptoms/features modeled
	Centrality of symptoms/features modeled
	Coherence of symptoms/features modeled: Do they co-occur clinically?
	How robust is the psychiatric diagnosis?
Construct validity	How well do we understand the model: Does it measure what it claims to measure?
	How well do we understand the disorder: Would clinicians agree with how it is being characterized?
	If there is a parallel human experimental model, how well has that model been validated?
	Do similar theoretical structures apply: Can homology be demonstrated in relation to psychological processes, anatomical localization, neurochemical mechanisms, or gene expression?

Assessment of Predictive Validity

The concept of predictive validity implies that manipulations known to influence the pathological state should have similar effects in the model: thus, manipulations known to precipitate or exacerbate the disorder should precipitate or exacerbate the abnormalities displayed in the model, while

manipulations known to relieve the disorder should normalize behavior in the model. In practice, the predictive validity of the animal models used in psychopharmacology is determined largely by their response to therapeutic drugs.

In this context, the primary requirements for predictive validity are that a valid test should be sensitive and specific: sensitivity means that the test should respond to effective therapeutic agents and specificity means that it should fail to respond to ineffective agents. Positive responses should occur at sensible doses, and should be demonstrable with a range of structurally diverse compounds, and where applicable, to nonpharmacological treatment modalities. Negative responses should be demonstrable with agents that cause behavioral changes similar to the therapeutic effect but achieve these effects by nonspecific actions (e.g., by changing locomotor activity). However, while sensitivity and specificity are crucial to an assessment of predictive validity, results may sometimes be distorted by species differences in drug kinetics or metabolism, which can lead to apparent discrepancies of drug action in animal models versus human patients.

In some circumstances, it may be possible to demonstrate that the relative potencies of different agents in a model correlate positively with their potencies in clinical use. This is potentially a powerful test, provided that there is sufficient variation among the chosen drugs in their clinical potencies. However, it can generate trivial data if the analysis fails to sample a range of chemically distinct compounds. For example, the positive correlation between the clinical potency of benzodiazepines and their performance in several animal models of anxiety (Anxiety, animal models) serves only to confirm that these drugs act at the same receptor.

There will always be a group of drugs for which, through a shortage of research, there is uncertainty over their status as clinically effective or ineffective. Moreover, the clinical classification of drugs as active or inactive may sometimes be incorrect. Drugs thought to be active on the basis of early open trials are frequently found to be inactive in later well-controlled tests; conversely, a drug may appear to be inactive because the emergence of side effects prevents its administration at adequate dosages, a problem that is less likely to arise in an animal model. It follows that the failure of an animal model to predict accurately will tend to weigh against the model, but may sometimes call instead for a reevaluation of the clinical wisdom. This illustrates an important principle: that the validity of a model is absolutely limited by the quality of the clinical information available to describe the condition modeled.

Assessment of Face Validity

Face validity refers to a phenomenological similarity between the model and the disorder modeled. On the one hand, the model should resemble the disorder; on the other, there should be no major dissimilarities. The checklist approach to psychiatric diagnosis adopted by the Diagnostic and Statistical Manuals of the American Psychiatric Association (DSM) provides a useful starting point for enumerating areas of potential comparison. In DSM, psychiatric diagnoses are established by reference to a checklist of core symptoms and a further checklist of subsidiary symptoms, with a requirement to demonstrate the appropriate number of symptoms from each list. If several points of similarity are demonstrable between a model and the disorder, then it is necessary to ask whether the cluster of symptoms identified forms a coherent grouping that might realistically be seen in a single patient, or whether they are drawn from a variety of diagnostic subgroups. Frequently, animal models focus on a single behavioral endpoint. In that case, it is important to assess whether this models a core symptom or a subsidiary symptom. For example, if the behavior in the model consists simply of a change in locomotor activity, this is likely to be of peripheral relevance to most psychiatric disorders. Similarly, the face validity of the model is less strongly supported if the symptom modeled is common to a several different psychiatric disorders (discriminant validity).

While a comparison with DSM provides an extremely useful starting point for assessment of face validity, other relevant comparisons should also be considered. For example, if the clinical condition only responds to chronic drug treatment (e.g., depression), then the model should also respond only to chronic drug treatment. Any neurobiological parallels between the model and the disorder also contribute to face validity.

Similarity between behavior in the model and the clinical symptom modeled should be demonstrated, rather than assumed. The demonstration of similarity requires a thorough experimental analysis, which, sadly, is often lacking. This can result in specious claims for face validity being advanced on the basis of unsupportable interpretations of behaviorally unsophisticated models. For example, many animal models of depression are based on a decrease in locomotor activity. (Depression: animal models) It is certainly possible that a decrease in locomotor activity might simulate symptoms of depression such as psychomotor retardation or loss of motivation, but without further behavioral analysis, these remain unsupported analogies. As a general rule, the less sophisticated the behavior (in the sense that its interpretation is less open to experimental investigation and analysis), the lower is the possibility of making a judgment of face validity.

A fundamental consideration in assessing face validity is that the comparison of symptoms between a model and the clinical condition can only proceed in respect of symptoms that are expressed behaviorally. Many symptoms of psychiatric disorders are only known from patients' verbal reports, and these symptoms, in principle, cannot be modeled. An example is suicidal ideation in depression. However hard we worked, we could never know if a rat was feeling suicidal (or to take an actual research example, if it was feeling a state of "despair"), (Behavioral despair) and therefore, this question falls outside the realm of scientific discourse: we simply cannot ask it. Nevertheless, it may sometimes be possible to express subjective symptomatology in behavioral terms. ▸Hallucinations are subjective phenomena that should be out of bounds for modeling in animals, but from careful observation of patients who are hallucinating, a set of operational criteria was developed to define associated behavioral phenomena (such as staring intently at an invisible object), thus enabling the inclusion of hallucinations as symptoms that in principle could be simulated in animal models of schizophrenia. (Schizophrenia: animal models) The rule, then, is that if a symptom can be expressed behaviorally and defined operationally, we can attempt to model it, but if it can only be expressed verbally, we cannot.

It is also important to remember that most DSM diagnoses are poorly established hypothetical constructs that can change radically between successive revisions of the manual. Again, the assessment of the validity of animal models is limited by the quality of the clinical data.

Assessment of Construct Validity

In order to evaluate the theoretical rationale of an animal model (construct validity), we require a theoretical account of the disordered behavior in the model, a theoretical account of the disorder itself, and a means of bringing the two theories into alignment. This can only be done if the clinical theory occupies an appropriate framework, which uses terms and concepts applicable also to subhuman species. Clearly, the subjective dimension of psychopathology cannot be central to such a theory, since subjective phenomena in animals are for most practical purposes outside the realm of scientific discourse. However, at the level of the cognitive processes underlying psychopathology, and the neurobiological mechanisms that underlie those cognitive processes, the possibility exists of constructing parallel theories. It follows from this analysis that the assessment of construct validity involves a number of relatively independent steps.

First, the theoretical account of behavior in the animal model requires evaluation. Just how well do we understand the model? Does it measure what it claims to measure? For example, if an animal model of depression is conceptualized as a decreased ability to respond to rewards, then at the very

least, it must be convincingly demonstrated that the decrease in rewarded behavior cannot be explained by, for example, sedative effects or a nonspecific decrease in consummatory behavior (Depression: animal models). Similarly, an animal model of dementia must demonstrate that performance failures result from a disorder of learning or memory, rather than from nonspecific causes, and further work should seek to characterize the specific memory processes involved. (Rodent models of cognition; Primate models of cognition)

In some areas, human experimental procedures have been developed that are based on procedures used in animal studies. However, demonstrating that a similar psychological process occurs in humans and animals is of limited value, since its role in the disorder also needs to be demonstrated. For example, some groups of schizophrenic patients show sensorimotor gating deficits that are very similar to those seen in animal models of schizophrenia: however, the contribution of sensorimotor gating deficits to schizophrenia remains uncertain (Prepulse inhibition, Latent inhibition). It will be clear that a detailed consideration of the human disorder forms an essential step in the evaluation of animal models, and that the relatively poor state of theoretical understanding of most psychopathologies places an upper limit on construct validity.

Recent developments in neuroimaging and psychiatric genetics may help to decrease the difficulty of establishing homology between animal models and psychiatric states. A major focus of work with animal models has been to establish the brain areas responsible for the behavioral changes, and neuroimaging methods can now provide similar information for psychiatric states, making it possible to evaluate in a much more precise manner whether common mechanisms are involved. (Magnetic resonance imaging: functional) Similarly, the identification of susceptibility genes and endophenotypes can now be translated directly into genetically modified animal models. (Genetically modified animals) This is a rapidly developing area of research, and it is likely that it will be used increasingly to develop animal models of psychopathology that by definition will have a degree of construct validity.

Cross-References

▸Hallucinations
▸Phencyclidine

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Anticholinergics

Definition

Group of drugs that impair cholinergic neurotransmission. The anticholinergics benztropine, biperiden and trihexyphenidyl are used to counteract extra-pyramidal side-effects of antipsychotics. They also reduce side effects when Parkinson's disease is treated with dopamine agonists and precursors.

Like the prototypical anticholinergics atropine and hyoscine, these agents act as antagonists at muscarinic acetylcholine receptors. Quite different groups of anticholinergics act at nicotinic receptors such as those in autonomic ganglia, the central nervous system and the neuromuscular junction.

Antipsychotic Drugs

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Synonyms

Neuroleptics
▸Major tranquilizer

Definition

Antipsychotics are drugs used to treat all kinds of psychoses, although the best evidence for their clinical effects stems from studies in the treatment of schizophrenia.

Pharmacological Properties

History

Antipsychotics, as we use the term now, were introduced into clinical psychiatry in the 1950s. They were originally called neuroleptics, a term still broadly used in medical jargon which is derived from Greek and loosely translated as "grasping the nerve." This reflects the fact that originally the sedative effects of these drugs were in the foreground of clinical interest. This was also the origin of the American term "major tranquilizers."

Over the last two decades antipsychotics has become the preferred term for this class of drugs based on their main indications and clinical effect. While it was originally felt that antipsychotic efficacy was inextricably linked to extrapyramidal motor side-effects (EPS), the introduction of ▸clozapine in the early 1970s demonstrated that this was not the case, as this drug proved to be an excellent antipsychotic with only a minimal risk to induce EPS. This also triggered a new classification of antipsychotics, which had so far been differentiated either by their chemical structure (e.g., ▸phenothiazines, ▸thioxanthenes, and ▸butyrophenones) or their affinity to the dopamine D2 receptor (high and low potency neuroleptics). The fact that clozapine was found to be an effective antipsychotic without inducing motor side-effects

was considered an "anomaly," and the term "atypical" was coined to describe clozapine and to differentiate it from the older "typical" drugs with their considerable potential for such adverse events. Consequently, antipsychotics which were developed following clozapine's introduction and which shared at least some of its characteristics were also subsumed under the category "▸atypical antipsychotics." It soon became clear that "atypical antipsychotics" represent a rather inhomogeneous group, both from preclinical and clinical pharmacological perspectives. As the receptor pharmacology of these drugs is complex and provides no solid basis for differentiation, the field agreed upon classifying these drugs based upon a less contentious base, namely a more historical dimension. Thereby, all drugs developed until the advent of clozapine were called ▸first-generation antipsychotics (or sometimes "classical" or "traditional") while the drugs that were introduced after clozapine and shared its low risk for EPS are now called ▸second-generation antipsychotics. We are now on the threshold of a third-generation of antipsychotics, initiated with the registration of ▸aripiprazole, the first licensed antipsychotic which is not a D2 antagonist.

Mechanisms of Action

It took about 10 years after the clinical efficacy of these drugs had been established until it was realized that antipsychotics block ▸dopamine receptors. This finding can be seen as the cornerstone of the dopamine hypothesis of schizophrenia. More than adecade later, (Seeman et al. ▸13) published their classic paper on the correlation between D2 dopamine receptor affinity and clinically effective doses of antipsychotics, demonstrating that drugs with high receptor affinity required lower doses than drugs with lower affinities. All currently licensed antipsychotics with the exception of aripiprazole, a partial D2 agonist, block postsynaptic dopamine D2 receptors. The fact that most of these drugs also influence other receptor systems has given rise to a number of alternative attempts to achieve antipsychotic effects. The most prominent targets were various subtypes of the serotonin receptor (e.g., 5HT2A, 5HT1A) and lately the glutamatergic system, including both ionotropic and metabotropic receptors (Miyamoto et al. ▸11).

Countless clinical and preclinical experiments link the effects of antipsychotics to the dopaminergic system. In very general terms, the acute administration of antipsychotics leads to an increased firing rate and neurotransmitter turnover in dopaminergic neurons while these effects are reversed after chronic administration (Grace ▸5). In this respect older drugs, such as ▸haloperidol, are different from newer ones such as clozapine insofar as haloperidol demonstrates these characteristics both in neurons originating in the substantia nigra (A9 dopaminergic neurons) as well as in those

which project from the ventral tegmentum (A10 neurons) while clozapine only blocks A10 neurons. This has been replicated many times using different electrophysiological, neurochemical, and imaging techniques and is considered the reason why clozapine exerts antipsychotic effects without affecting the motor system (Miyamoto et al. ▸11).

Clinically, the introduction of single photon emission tomography (SPECT) and positron emission tomography (PET) have provided the most relevant neurobiological leads into the effects of antipsychotics in humans. All available antipsychotics bind to striatal (and possibly extrastriatal) dopamine receptors in varying degrees. A dose–response relationship between human D2 receptor affinity and clinical profile is very likely, albeit it is challenged by the findings that the highly effective antipsychotic clozapine and also ▸quetiapine only loosely bind to this receptor (Stone et al. ▸14).

In summary, all evidence taken together clearly points to a disruption of dopaminergic function in schizophrenia patients and strongly suggests that a restoration of balance in this system contributes to the therapeutic efficacy of antipsychotics.

As outlined earlier, other receptor systems have also been investigated in this context. As clozapine has high affinity to a number of other neurotransmitter receptors (including serotonin, histamine, and noradrenaline), these systems have been explored regarding their potential contribution to the drug's benefit–risk profile. The hypothesis most vigorously explored was the one that linked its serotonin (5HT2) antagonist properties to the clinical profile. In conjunction with previous preclinical research which had found that serotonin antagonists can counteract extrapyramidal motor side-effects of neuroleptics, Meltzer et al. (▸10) formulated the hypothesis that 5HT2 antagonism which is proportionally larger than D2 antagonism is responsible for the advantages that clozapine and all other drugs sharing this profile have over the older drugs in terms of lower EPS risk. In addition, they and other authors feel that these pharmacological characteristics also contribute to enhanced clinical efficacy, especially with regard to negative symptoms and cognitive impairment. Although an intriguing and well thought through hypothesis, it is somewhat challenged by the pure dopamine antagonist ▸amisulpride which has no direct effects on the serotonergic systems, yet shares a lot of the clinical effects with 5HT2/D2 antagonists (McKeage and Plosker ▸9).

The glutamate system is intricately linked with dopaminergic neurotransmission throughout the central nervous system (CNS), a topic reviewed by Carlsson et al. (▸2). It functions as a modulator of dopaminergic neurotransmission. This has led to a number of clinical experiments aiming at investigating drugs that do not directly act via the dopaminergic systems.

Both the glycine sites of NMDA receptors and metabotropic glutamatergic receptors have been the targets of such investigations. Clinical studies are encouraging but have not yet led to licensed medications (Miyamoto et al. ▸12).

Other neurotransmitter systems have mostly been considered in the context of drug safety. Many antipsychotics which block noradrenergic α1 receptors have been found to affect blood pressure. Antihistamine effects have been related to sedation and weight gain, just to provide a few examples.

Animal Models

There is no reliable and valid animal model for schizophrenia. All available models are either derived from the dopamine hypothesis of schizophrenia or from the actions that effective antipsychotics induce in laboratory animals. Many of them are related to non-therapeutic effects of antipsychotics such as those which affect the motor system. At the most, we may optimistically assume that these models are in some approximation to the clinical syndrome of the disorder. Nevertheless, animal models, imperfect as they may be, are still a cornerstone of antipsychotic drug development (Lipska and Weinberger ▸8). Conditioned ▸active avoidance is a classic among these models. All antipsychotics block conditioned avoidance and this test is therefore one of the early screening experiments in the development of potential antipsychotics.

Another set of experiments involve the various motor effects of this class of drugs. Spontaneous locomotor activity as well as pharmacologically enhanced psychomotor activity is usually decreased after the administration of antipsychotic drugs. First- and second-generation antipsychotics are nicely differentiated by the dose needed to induce catalepsy, which is a good indicator for clinical EPS risk.

More recent models which can also be performed in humans include various variants of sensory motor gating studies. One example for these is prepulse inhibition (PPI), which is based on the finding that a weak prepulse reduces the startle reflex to a given, usually acoustic, stimulus. It is seen as part of the information processing capabilities of the CNS. PPI can be disrupted by both dopamine agonists and NMDA antagonists, thereby providing a model within the dopamine/glutamate hypothesis of schizophrenia. As antipsychotics restore PPI in animals in which it has been disrupted, such sensory motor gating models are also seen as indicative of potential antipsychotic effects.

Pharmacokinetics

Antipsychotics are generally well absorbed and most of them are metabolized by hepatic cytochrome P450 isoenzymes. They are generally highly

lipophilic and therefore cross the blood-brain barrier well and accumulate in fatty tissues. The benzamides ▸sulpiride and ▸amisulpride are an exception to these rules.

The elimination half-lives of antipsychotics are distributed over a wide range between a few hours (▸quetiapine) and days (aripiprazole). Steady-state levels differ accordingly, but as a rule of thumb once-daily dosing is possible. It is important to note that elimination from the brain and the drugs' target organs has been shown to be much slower than from plasma (Gruender ▸6).

Given that all drugs with the exception of the benzamides are metabolized via cytochrome isoenzymes in the liver, the potential for interactions with other drugs which compete for these enzymes needs to be considered. Pharmacodynamic interactions are to be expected when antipsychotics are coadministered with drugs that target the same receptor systems, either centrally or peripherally. These include drugs with antihistamine and antiadrenergic effects which can lead to a potentiation of sedation, weight gain, or hypotensive adverse events.

Efficacy

Next to antipsychotic effects, i.e., reducing delusions and ▸hallucinations, most antipsychotics also have sedative properties. Furthermore, they have been shown to reduce negative symptoms, enhance cognitive functions, ameliorate affective symptoms (both manic and depressive) in patients suffering from schizophrenia and, most likely as a secondary effect, improve the quality of life and psychosocial reintegration (Miyamoto et al. ▸11). Although most research with antipsychotics has been performed in schizophrenia patients, the therapeutic actions of these drugs extend beyond this diagnosis. Indications include mania, psychotic depression, ▸schizoaffective disorder, bipolar depression, psychotic symptoms in the context of organic disorders from delirium to dementia, personality disorders, and treatment-resistant obsessive compulsive disorder, just to list the better researched disorders. As most of these are be covered in other entries, only general treatment principles in schizophrenia patients are briefly reviewed.

Recent evidence indicates that the onset of antipsychotic action in schizophrenia can be seen within days of commencing treatment (Agid et al. ▸1), although it may take up to 6 months to achieve full remission of symptoms. Close to two thirds of first-episode schizophrenia patients reach symptom remission within this time if the duration of previously untreated psychosis is not too long. Response patterns become less favorable with increasing chronicity of the disorder. Next to acute symptom control and stabilization, antipsychotics also have powerful relapse-preventing properties (Kane ▸7). Regularly taking medication over long periods of time protects about 80%

of patients from a psychotic relapse. Having said that, compliance is one of the major challenges of the long-term management of schizophrenia (Fleischhacker et al. ▸4). To aid uninterrupted dosing, depot antipsychotics that are injected at regular, long intervals have been developed. So far ▸risperidone and ▸olanzapine are the only second-generation antipsychotics available for this method of administration (Fleischhacker ▸3).
Clozapine plays a special role in the management of schizophrenia. On the one hand, it is the drug of choice in patients with a treatment-resistant course of the disorder; on the other hand, it has a 1% risk to induce agranulocytosis which makes it a third line drug despite its excellent efficacy (Tandon et al. ▸15).

Safety/Tolerability

For first-generation antipsychotics, sedation as well as acute and tardive extrapyramidal motor side effects represented the biggest safety obstacles that also translated into tolerability and compliance problems. Next to that, these drugs, depending on their receptor profiles, induced a number of other adverse events including anticholinergic side effects, orthostatic hypotension, weight gain, hormonal aberrations including sexual disturbances, dermatologic problems including acne-like manifestations and photosensitivity, disturbances of gastrointestinal motility, hematological side effects, cardiac arrhythmias, seizures, and the neuroleptic malignant syndrome, just to name the clinically most relevant. Apart from potentially life-threatening adverse events such as clozapine-induced agranulocytosis, tachyarrhythmia, and the neuroleptic malignant syndrome, many of these side effects constitute problems affecting subjective tolerability rather than objective health risks. Prevalence rates differ considerably between drugs, and the incidence of these side effects is difficult to predict on an individual level. Therefore, patients treated with antipsychotics have to be well informed and monitored regularly.
Second-generation antipsychotics as a group have a considerably lesser risk to induce EPS than the older drugs. This applies to both frequency and severity of acute and chronic motor side effects. Some of these drugs, most notably clozapine and olanzapine, have a substantial propensity to induce weight gain and metabolic disturbances such as hyperlipidemia and reduced insulin sensitivity. Apart from these concerns the newer drugs appear to be tolerated appreciably better than traditional neuroleptics. Clearly, despite this, the same recommendations regarding patient information and monitoring must be followed (Miyamoto et al. ▸11).

Conclusion

In summary, antipsychotics represent a crucial component of the pharmacotherapeutic options in psychiatry. A large array of effective drugs is available. Antipsychotics are employed over a broad range of indications with a very favorable benefit–risk profile. It is hoped that their main therapeutic limitations, namely efficacy beyond psychotic symptoms, will be overcome with the exploration of pharmacologic mechanisms which extend beyond the dopamine system.

Cross-References

- ▸Butyrophenones
- ▸Clozapine
- ▸Extrapyramidal Motor Side Effects
- ▸First-Generation Antipsychotics
- ▸Phenothiazines
- ▸Second and Third Generation Antipsychotics
- ▸Thioxanthenes

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Anti-Parkinson Drugs

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Definition

Parkinson's disease (PD): a syndrome defined in life by clinical criteria involving tremor at rest, rigidity, slowness and paucity of movement, altered posture, gait and balance with the absence of "atypical" features (Lang and Lozano ▸6a,b). It is defined at autopsy by strict pathological criteria including the loss of neurons in the pars compacta of the substantia nigra, locus ceruleus and dorsal motor nucleus of the vagal nerve, and the presence of Lewy bodies.

Pharmacological Properties

Although Parkinson's disease (PD) is classified as a "movement disorder", it should also be considered as a "neurobehavioral" disorder. The diagnosis of PD is based on the presence of clinical criteria having to do purely with movements and the absence of exclusionary or atypical features, laboratory tests being of little or no value. Nevertheless, the most devastating aspects of PD are more often behavioral. Other nonmotor problems, such as sympathetic dysfunction and sleep disorders have only attracted clinical and research attention in the last few years. For perspective two studies, one a large retrospective review in Australia, and the other, a county wide prospective study with formal testing in Norway, both concluded that by the time of death, 80% of PD patients are demented. In addition, at any point in time, somewhere between 30 and 50% are depressed; 40% suffer from anxiety; 40% with apathy; 30% of drug treated patients with visual hallucinations; 5–10% of drug treated patients with delusions; and over 30% of newly diagnosed patients, untreated, suffer from fatigue unrelated to depression or the severity of their motor dysfunction.

PD in simplistic terms is often understood as a dopamine deficiency disease. While it is this, there are also abnormalities in multiple neurotransmitter systems. The dopamine motor system is the best understood and deficiencies here do cause many of the major motor problems in PD, including bradykinesia, rigidity, tremor, and gait dysfunction. Improving dopamine transmission has been the focus of modern drug therapy, starting with the introduction of the first rational designed treatment for a neurological disorder, l-Dopa.

l-Dopa, combined with an aromatic amine decarboxylase inhibitor (AADI), carbidopa, has been the mainstay of the treatment of PD since it was introduced in the late 1960s (Cotzias et al. ▸3). The AADI reduces the amount of l-Dopa converted in the bloodstream to ▸dopamine, dramatically reducing the problem of nausea which was frequent when l-Dopa was used alone. l-Dopa is the precursor to dopamine, and in the chemical path that converts tyrosine to dopamine, l-Dopa occurs after tyrosine hydroxylase, the rate-limiting enzyme. l-Dopa is taken up by the remaining nigral cells and converted to dopamine. l-Dopa improves slowness, rigidity, akinesia, and gait, but does not usually improve speech, freezing, balance, and its effect on tremor are unpredictable. In addition to the existence of symptoms not responsive, and therefore presumably not of dopamine deficiency origin, the disease progresses and drug manipulations are unable to keep up. As more dopamine secreting cells die, the drug becomes less effective.

Long-term use of l-Dopa often leads to motor complications, which are not seen when other drugs are used in PD patients who have never been exposed

to l-Dopa (Fox and Lang ▸3). These include dyskinesias induced by the drug, as well as markedly variable responses to the drug with "on" periods, when patients have a good response to the drug, and either predictable or unpredictable "off" periods when the medicine stops producing benefit.

Other ways of enhancing dopamine transmission involve reducing dopamine breakdown or altering l-Dopa pharmacokinetics. The monoamine oxidase-b inhibitors (MAOb-I), selegiline and rasagaline, are both used as adjunctive agents to enhance the activity of dopamine. These drugs work both peripherally, in the bloodstream to block the degradation of l-Dopa and centrally, in the brain to reduce degradation of dopamine. In the brain, dopamine is primarily resorbed by the presynaptic neuron though the dopamine transporter, but about 10% is broken down in the synaptic cleft by monoamine oxidase b and catechol-o-methyltransferase. Blocking the degradation of dopamine in the synapse allows more dopamine to activate the dopamine receptors, thereby increasing the potency of the dopamine stimulation as well as its duration of action. Both drugs are therefore approved for the purpose of increasing "on" time in patients who suffer from clinical motor fluctuations in reponse to l-Dopa. Rasagaline is also used as a monotherapeutic drug, presumably acting in the same fashion, enhancing dopamine stimulation. Its benefits are less than those typically seen with dopamine agonist monotherapy, but its side effect profile in these patients is not much different than that of placebo.

The greatest interest in the MAO-b inhibitors lies in their possible disease "modifying" effect that is, slowing of disease progression. There is suggestive data supporting this contention for rasagaline. The first large study to slow PD progression used selegiline, and while initially deemed a positive study, was reinterpreted in light of its mild, but statistically significant symptomatic effects. The rasagaline studies used a different research paradigm to avoid this confound (Olanow et al. ▸10).

Although nonspecific MAO inhibitors hold the potential for a large number of drug and food interactions, all of these are due to MAO-a inhibition. At the doses approved for PD, the MAO-b inhibitors are free of MAO-a inhibition and are quite safe, free of tyramine interactions, and of interactions with selective serotonin reuptake inhibition (SSRI) antidepressants. However, there is a concern about an unexplained, potentially fatal interaction with meperidine.

In monotherapy, rasagaline has no significant behavioral effects. When used adjunctively with l-Dopa, all l-Dopa side effects are enhanced.

The catechol-o-methyltransferase inhibitors (COMT-i) block the enzyme, catechol-o-methyltranserfase that, along with MAO-b, breaks down dopamine. There are two such drugs used in USA, tolcapone and entacapone,

neither of which crosses the blood-brain barrier to an appreciable degree. These drugs therefore exert their effect on the pharmacokinetics of l-Dopa. By themselves, these drugs do not have any known effect on PD. Tolcapone may cause severe liver damage in a very small percentage of users. Entacopone is less effective, but is free of liver toxicity.

Since dopamine does not cross the blood-brain barrier, dopamine agonists have been used to compensate. These medications, bromocriptine, pramipexole, ropinerole, lisuride, rotigotine, cabergoline, and apomorphine, all directly stimulate D2 receptors (along with variable potencies at other dopamine receptors), and produce motor benefits comparable to l-Dopa at the early stages of the disease, but are less effective for the long-term. Unlike l-Dopa, these medications do not cause long-term motor side effects such as "wearing off", in which the benefit of l-Dopa declines before the next dose, unpredictable fluctuations, in which the l-Dopa doses last highly variable periods of time, or dyskinesias, which are involuntary movements, usually choreic in nature (Constantinescu et al. ▸2; Jankovic and Stacy ▸5). Unfortunately, these drugs produce more short-term side effects including hypotension, ▸hallucinations, nausea, and generally need to be supplemented with l-Dopa within a few years. The dopamine agonists are often used as initial therapy to postpone the long-term side effects of l-Dopa, or may be added to l-Dopa as its benefits decline.

Anticholinergic drugs were the mainstay of drug therapy of PD until the development of l-Dopa. These drugs are helpful in reducing tremor and rigidity, but are thought to provide little benefit in slowness, or gait, two of the most functionally debilitating symptoms in PD. Additionally, these drugs have profound side effects that make them difficult to use, particularly in older people. These side effects are very common, and include dry mouth (which may be useful to reduce drooling), constipation, memory dysfunction, urinary retention, blurred vision, hallucinations. These drugs are primarily used in younger patients, who tolerate them better, particularly where tremors and drooling are problems.

Amantadine was first reported in 1972 to ameliorate the motor symptoms of PD as a serendipitous observation when used to treat influenza in people with PD. The drug had been thought to work by increasing dopamine secretion or by blocking acetylcholine, but it is currently believed to work as an NMDA glutamate antagonist. It is helpful for all aspects of PD, including tremor, but is not as effective as dopamine agonists or l-Dopa. It has been increasingly used in recent years after it was shown to reduce l-Dopa induced dyskinesias in PD patients, without a reduction in the other drugs used to treat PD motor symptoms. Amantadine may induce psychotic symptoms, delirium, and mild anticholinergic side effects, as well as livedo

reticularis (which has no negative consequences other than appearance) and pedal edema (Pahwa et al. ▸11).

Although dementia is a common problem in PD, only one drug has been approved for its treatment (Burn et al. ▸1). Most authorities believe that the three cholinesterase inhibitors probably work about equally well, but this is not based on clinical data. Since Parkinson's disease dementia (PDD) patients have a greater cholinergic deficit than Alzheimer's patients, it was assumed that the cholinesterase inhibitors might therefore work better than in Alzheimer's disease (AD). This has not been borne out by clinical observation. The mechanism of action of these drugs is presumed to be the same in PDD as in AD, blocking the degradation of acetylcholine. However, the benefits of rivastigmine in PDD are extremely limited, and most patients do not sustain sufficient benefits to justify the cost of the drug. Memantine, which is the only noncholinesterase inhibiting drug approved for treating dementia in AD, shares NMDA glutamate antagonism with amantadine, but it has not been shown to produce any motor benefit in PD. Rivastigmine is more helpful for concentration, apathy, and hallucinations than it for cognitive and memory problems (Burn et al. ▸1).

No antipsychotic is approved for treating hallucinations and delusions in PD in USA, but ▸clozapine, at extraordinarily low doses, is approved for this use in other countries based on two multi-center double blind placebo controlled trials (Parkinson study group ▸12). In USA, ▸quetiapine has been recommended as the drug of first choice by an American Academy of Neurology task force, despite the fact that no double blind trials, support its efficacy (Miyasaki et al. ▸9). Clozapine is the task force's second line recommended drug.

No antidepressant has been approved for treatment of depression in PD, and none has been adequately tested to confirm benefit. Some high quality data published in 2009 indicates that depression in PD may be medication responsive, and that tricyclics may be more effective than selective serotonin reuptake inhibibitors (SSRI) (Menza et al. ▸8). Although the SSRI's may produce tremor or parkinsonism, they have been well tolerated in PD.

Conflict of interests: JHF has received remuneration from the following companies in the past 12 months either for consultation, lectures, or research: Acadia Pharmaceuticals, Astra-Zeneca, Novartis, Glaxo, Ingelheim-Boehringer, Teva, Valeant, Cephalon, EMDSerono, Schwartz.

Novartis makes clozaril (clozapine)

Astra-Zeneca makes Seroquel (quetiapine)

Acadia is testing pimavanserin as an antipsychotic for PD

Cross-References

- ▸Hallucinations
- ▸Hallucinogens

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Antipsychotic Medication: Future Prospects

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Synonyms

Ongoing and future development of antipsychotics (neuroleptics)

Definition

Antipsychotic medications are a group of psychoactive drugs used to treat psychosis, which is typified by ▸schizophrenia. The currently available antipsychotic medications show some benefit to patients, but have considerable limitations in terms of efficacy and side effects. The development of new antipsychotic compounds with novel mechanisms of action is being pursued based on specific strategies and guided by various pathophysiologic hypotheses. This article focuses on novel goals and targets for therapeutic intervention and potential strategies for future development of antipsychotic medication.

Pharmacological Properties

Limitations of Currently Available Antipsychotic Medications

The introduction of newer second-generation antipsychotics (SGAs) represents an important advance in the pharmacologic treatment of schizophrenia since the advent of ▸chlorpromazine, the prototypical ▸first-generation antipsychotics (FGAs). However, current evidence suggests that the clinical benefits of SGAs in terms of efficacy are modest at best (Leucht et al. ▸5), and the effect sizes on ▸cognitive impairment are small. In the largest and longest effectiveness trial, the clinical antipsychotic trials of intervention effectiveness (▸CATIE) study, no substantial advantage for the SGAs was demonstrated over the FGA for the treatment of negative and cognitive symptoms (Lieberman et al. ▸6). Negative and cognitive symptom domains are recognized as a core feature of schizophrenia and play a greater role in poor functional outcome. Thus, it is obvious that there is a distinct need to identify and validate novel molecules that possess pharmacological profiles that better treat these symptom domains.

To date, the prototypical SGA ▸clozapine remains the "gold standard" antipsychotic drug because of a lower liability for ▸extrapyramidal motor side effects (EPS) and because it has proved superior to all other ▸antipsychotic drugs in efficacy (Leucht et al. ▸5), particularly in treatment-resistant schizophrenia. However, even with clozapine, a significant number of patients

are unresponsive to treatment and it carries a risk of serious side effects such as agranulocytosis, weight gain, and metabolic abnormalities. Because individuals with schizophrenia have many risk factors that may predispose them to poor health and excess mortality, safety and tolerability of antipsychotic medications are an essential treatment concern. Furthermore, remission and recovery rates for schizophrenia by the treatment with current antipsychotic medications are discouragingly low. Thus, it is important to pursue the development of more tolerable and more effective antipsychotics than clozapine. To expedite the clinical development of such drugs, biological or surrogate markers of the illness and treatment effects using chemical technologies (e.g., PET imaging) must be identified and validated to enable more efficient and reliable proof of efficacy of novel compounds.

Challenges of Future Drug Discovery

A number of mechanisms of action of antipsychotics have been explored during the past 30 years. However, it is still unclear as to what pharmacological profile of antipsychotic medication is necessary to show the highest efficacy and effectiveness without serious adverse effects in the treatment of schizophrenia and other psychosis. Moreover, there is still an ongoing debate as to whether drugs selective for single molecular target (i.e., "magic bullets") or drugs selectively nonselective for several molecular targets (i.e., "magic shotguns") will lead to new and more effective medications for psychosis (Agid et al. ▸1; Roth et al. ▸10).

All currently available antipsychotic medications target dopamine D2 receptors, but one example of new multitarget strategies is the utility of combined dopamine D2-like receptor antagonism and serotonin 5-HT1A receptor agonism (Jones and McCreary ▸4). It is suggested that the balance between D2 antagonism and 5-HT1A agonism may be critical in determining the efficacy of these compounds. In addition, further serotonergic strategies may be a key area of schizophrenia research such that combined activity at the D2 receptor with selective serotonin reuptake inhibitor, and the use of 5-HT2C receptor agonists, 5-HT6 receptor antagonists, or 5-HT7 receptor agonists may be of great interest in expanding treatment options (Jones and McCreary ▸4).

Recent antipsychotic research has examined agents that have no direct effect on the dopamine system, although most of them have indirect effects on dopaminergic pathways. For example, with the emerging evidence for glutamatergic dysregulation in schizophrenia, a number of agents with direct or indirect activity on the glutamate system are being investigated, especially for their potential impact on cognitive and negative symptom domains (Miyamoto et al. ▸8). Glutamate-based agents in various stages of development include agonists at the glycine allosteric site of the N-methyl-D-

aspartate (NMDA) receptor, glycine transporter 1 inhibitors, Group II metabotropic glutamate receptor agonists, α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA)/kainate receptor antagonists, and higher-potency ampakines. The putative antipsychotic action of these drugs has been studied as monotherapy and/or add-on treatment (Gray and Roth ▸3).

It has also been suggested that the central cholinergic system is involved in the cognitive deficits observed in schizophrenia, and enhanced cholinergic activity may improve these deficits (Miyamoto et al. ▸8). Currently available treatments which are potentially suitable for this purpose include acetylcholinesterase inhibitors (e.g., galantamine), partial muscarinic agonists (e.g., xanomeline), nicotinic agonists, and allosteric potentiators of nicotinic receptor function (Gray and Roth ▸3). These potential cognitive enhancers may be better suited to particular stages of schizophrenia, perhaps showing efficacy in early or later stages.

In recent years, significant progress has been made on elucidating various susceptibility genes in schizophrenia, including ▸dysbindin, neuregulin 1, catechol-O-methyltransferase (COMT), disrupted in schizophrenia 1 (DISC1), and others (Gray and Roth ▸3). Many of these genes appear to be associated with the control of synaptic plasticity and glutamate transmission, especially NMDA receptor function. Research on these molecules will allow for rational drug development in which drugs are developed on the basis of targets derived from theories of pathogenesis of the disease. However, the conundrum of single-target versus multitarget agents will remain at the forefront of drug development until the etiology of the illness is fully elucidated. In the near future, optimal treatment will probably include different therapeutic agents, each uniquely targeting a specific dimension of schizophrenia (Agid et al. ▸1). In other words, single-target agents will augment multitarget agents, and there is a possibility that novel biological agents will also be investigated (Nikam and Awasthi ▸9).

Recently, a growing body of evidence has demonstrated that some SGAs may increase or preserve neurotrophic factor levels, neurogenesis, neuronal plasticity, mitochondrial biogenesis, cell energetic, and antioxidant defense enzymes (Lieberman et al. ▸7). Moreover, specific SGAs can ameliorate the loss of gray matter in schizophrenic patients in the early stages. These neuroprotective properties of some SGAs have become more relevant in the light of the increasing acceptance by the field of a progressive pathophysiological process and possibly neurodegenerative process coincident with the onset of schizophrenia that may underlie the clinical deterioration. Ongoing research on the neuroprotective effects of antipsychotics may reflect another mechanism of action that antipsychotics can act through that is

clinically relevant and should stimulate the search for new agents for psychosis with novel mechanisms beyond the monoaminergic systems (Lieberman et al. ▸7).

New Preparations of Antipsychotic Medications

At present, antipsychotic medications are available as tablets, liquid concentrates, orally dissolving formulations, short-acting intramuscular (I.M.) preparations, or long-acting injection (LAI) preparations. Among them, several SGA LAI preparations have been and are being developed. By increasing the available treatment choices for clinicians and patients alike, new preparations such as drug-in adhesive transdermal patches and nasal spray are a welcome development. Researchers must study these preparations beyond the usual registration package.

Moving Toward the Future Individualized Treatment

There is a great need for the development of novel methods to identify optimum individualized treatment plans. In particular, the efficacy and tolerability of antipsychotics could be directly influenced by genetic variations in cytochrome P450 (CYP) enzymes. Their activity may also be influenced by genetic alterations affecting the drug target molecule, such as monoaminergic receptors, neurotransmitter transporters, and enzymes. In the future, genetic tests for the pretreatment prediction of drug metabolic status, antipsychotic response, and drug-induced side effects such as EPS and weight gain are expected to bring enormous clinical benefits by helping to chose the medication, adjust therapeutic doses, and reduce adverse reactions (Arranz and de Leon ▸2). Further development of genetic tests and pharmacogenetic research into genetically determined drug metabolic polymorphisms as well as pharmacogenomic strategies to the identification of novel factors influencing response would lead to a better understanding of the rational basis for the personalization of antipsychotic treatment. In addition, antipsychotic drugs may also be targeted to specific patient subgroups based on profiling and the identification of endophenotypes of schizophrenia. Clinical implementation of this practice may have a strong impact in reducing adverse effects and improving treatment adherence and efficacy (Arranz and de Leon ▸2).

Conclusion

Future drug discovery approaches will have to be truly revolutionary, but there is a hope that we could obtain novel antipsychotic drugs with greater efficacy and improved safety profiles. These drugs, however, alone may not produce a complete cure. It is essential that all of the pharmacologic tools should always be used in combination with psychosocial and psychother-

apeutic intervention to optimize overall quality of life and return patients to the best level of functioning.

Cross-References

▸Chlorpromazine
▸Cognitive Impairment
▸Dysbindin
▸Pharmacogenetics of Antipsychotic Drug Response in Schizophrenia
▸Pharmacogenetics of Drug Side Effects and Safety
▸Second and Third Generation Antipsychotics

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Antisaccade Task

Definition

An important variant of the prosaccade task, in which participants are required to saccade to the mirror image location of a sudden onset target. Healthy participants typically make errors (prosaccades toward the target) on around 20% of trials. This figure is increased in patients with lesions to the dorsolateral prefrontal cortex and patients with schizophrenia. The task indexes cognitive processes associated with goal activation and inhibitory control.

Aripiprazole

Definition

Antipsychotic drug of the third generation with partial agonist properties at dopamine D2 receptors, as well as at serotonin1A receptors, and in addition antagonist properties at serotonin2 receptors.

Cross-References

▸Second- and third-generation antipsychotics

Asenapine

Definition

Asenapine is a 2nd generation antipsychotic binding to 5HT, D1 and D2 receptors, recently approved for the management of schizophrenia by the FDA.

Cross-References

▸Second- and third-generation antipsychotics

Atypical Antipsychotic Drugs

Synonyms

Second- and third-generation antipsychotics

Definition

All conventional antipsychotics (also called first-generation antipsychotics) share the central property of dopamine 2 receptor antagonism and, in association with this property, can cause extrapyramidal side effects (EPS). Atypical antipsychotics are so-called because they generally have a lower propensity to cause EPS than the older agents; the exact reason for this is unknown but is believed to be due to the fact that these agents have the additional property of 5HT2A antagonism and/or dopamine 2 partial agonism (as opposed to antagonism).

Cross-References

▸Schizophrenia

Benperidol

Definition

Benperidol is an older antipsychotic belonging to the butyrophenone class that blocks dopamine D2 receptors with high affinity. While it has similar properties to ▸haloperidol, benperidol has been used primarily for the treatment of deviant antisocial sexual behavior. Potential side effects, as with other neuroleptics, include extrapyramidal symptoms (EPS), QT prolongation, and hyperprolactinemia.

Cross-References

▸First-Generation Antipsychotics

Benztropine

Definition

Benztropine is an anticholinergic drug used in the management of extrapyramidal motor side effects, especially drug induced Parkinsonism.

Cross-References

▸Anticholinergics
▸Extrapyramidal Motor Side Effects

Blonanserin

Synonyms

AD-5423

Definition

Blonanserin is a second-generation (atypical) antipsychotic drug indicated for the treatment of schizophrenia. It belongs to a series of 4-phenyl-2-(1-piperazinyl)pyridines and acts as an antagonist at D2, D3, and 5-HT2A receptors. Its affinity for D2 receptors is approximately six times greater than that for 5-HT2A receptors. It has low affinity for α1, 5-HT2C, H1, and M1 receptors, but displays relatively high affinity for 5-HT6 receptors. Its safety profile compared favorably with haloperidol, particularly with respect to prolactin elevation and the frequency of extrapyramidal motor side effects.

Cross-References
▸Extrapyramidal Motor Side Effects
▸Haloperidol
▸Schizophrenia
▸Second-Generation Antipsychotics

Bradykinesia

Definition
Slowed movements.

Cross-References
▸Extrapyramidal Motor Side Effects

Brain Abnormalities

Definition
Already in the early 1900s, imaging techniques were available to investigate the human brain *in vivo*. In 1970, a first CT study was published, which showed brain abnormalities in patients with ▸schizophrenia and in 2000 a cross-sectional meta-analysis convincingly showed that brain volume changes are present in schizophrenia. Nowadays, schizophrenia is generally known as a disease associated with changes in brain morphology.

Cross-References
▸Extrapyramidal Motor Side Effects

Bromperidol

Definition
Bromperidol is an antipsychotic drug used to treat the symptoms of schizophrenia. It is a first-generation drug and does therefore have a stronger tendency to induce motor side effects than many newer antipsychotics. Bromperidol can be administered as a depot given intramuscularly every few weeks, which gives long-term antipsychotic treatment and improves compliance.

Cross-References

▸First-Generation Antipsychotics
▸Schizophrenia

Butyrophenones

Definition

A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in the treatment of schizophrenia. The most prominent member of this category is ▸haloperidol.

Cross-References

▸First-Generation Antipsychotics

Cariprazine

Definition

A drug with potential antipsychotic and mood-stabilizing properties and now in Phase III clinical trials. Chemically it is trans-N-[4-[2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl]cyclohexyl]-N',N'-dimethylurea hydrochloride. It has a complex profile of partial agonist and antagonist effects at different types of dopamine receptor as well as other actions, e.g. at some serotonin receptors.

Cross-References

▸Second- and third-generation antipsychotics

Carpipramine

Definition

Carpipramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class indicated for the treatment of schizophrenia, particularly for negative symptoms. It has been found that carpipramine, and its pharmaceutically acceptable salts, possess antagonist properties with respect to D2 and 5-HT2 receptors, and are also useful in the treatment of depression, anxiety, and sleep disorders. It can induce insomnia, agitation, and extrapyramidal motor side effects, but it displays generally low toxicity.

Cross-References

▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics
▸Schizophrenia

Catalepsy

Definition

A state seen in schizophrenia, other disorders of the nervous system and drug-induced dissociated states, in which unusual postures or facial expressions are maintained, regardless of external stimuli.

Cross-References

▸Schizophrenia

Catatonia

Definition

Catatonia includes both psychic and motor disturbances and is classically associated with psychiatric conditions (such as ▸schizophrenia, bipolar disorder, posttraumatic stress disorder, and depression). It can also be caused by dissociative agents, abuse of other drugs, and many medical conditions including encephalitis, autoimmune disorders, strokes, metabolic disturbances, and benzodiazepine withdrawal.

The DSM-IV criteria for catatonia include at least two of the following: motor immobility as evidenced by catalepsy and waxy flexibility or stupor; excessive and purposeless motor activity not influenced by external stimuli; extreme negativism (motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism; peculiarities of voluntary movement as evidenced by posturing, stereotyped movements, prominent mannerisms, or prominent grimacing; echolalia (repetition of the words or phrases of another person) or echopraxia (involuntary repetition or imitation of the observed movements of another person).

Cross-References

▸Schizophrenia

CATIE

Synonyms

Clinical Antipsychotic Trials of Intervention Effectiveness

▸Clinical Antipsychotic Trials of Intervention Effectiveness Study

Definition

A study that compares perphenazine with the SGA in the treatment of schizophrenia. General conclusion was that perphenazine was as effective and well tolerated as SGA.

Cross-References

▸Perphenazine

▸Second and Third Generation Antipsychotics

▸Schizophrenia

Chlorpromazine

Definition
Chlorpromazine was the first drug developed with a specific antipsychotic action. It is considered to be the first of the first-generation (typical) antipsychotics. Chlorpromazine is the prototype for the phenothiazine class antipsychotic and has relatively low potency at dopamine D2 receptors as well as antagonism of muscarinic, histaminergic, and adrenergic receptors.

Cross-References
▸First-Generation Antipsychotics
▸Phenothiazines

Chronic Disappointment Reaction

Synonyms
Demoralization syndrome

Definition
A syndrome involving lowered or dysphoric mood that occurs in response to a perceived unpleasant situation or set of experiences that is repetitive or enduring. The offending experience typically represents an assault on the individual's self-concept or self-esteem. The person experiencing a chronic disappointment reaction may feel overmatched by the circumstances and may feel helpless and/or hopeless in terms of prospects for improving the situation. Such a person may engage in any of a number of attitudes or behaviors to protect his or her feeling state from further adverse impact – such as avoidance, disinterest, or psychosocial withdrawal. The person having the chronic disappointment reaction may or may not be fully aware of, or fully able to explain, the issue or issues to which the reaction is in response. A chronic disappointment reaction can continue with an open-ended duration.

Clinical Antipsychotic Trials of Intervention Effectiveness Study

Synonyms
▸CATIE

Definition

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was the largest, longest, and most comprehensive independent, three-phase, clinical trial ever conducted to examine existing pharmacotherapies for schizophrenia. The trial was funded by NIMH and intended to be "pragmatic", involving a representative sample of 1,493 schizophrenic patients from various real-life outpatient settings. The primary outcome measure was time to all-cause drug discontinuation that captured both efficacy and tolerability. Subjects in the CATIE trial were randomized in a double-blind fashion to treatment with olanzapine, quetiapine, risperidone, ziprasidone, or the mid-potency first-generation antipsychotic perphenazine for up to 18 months of treatment.

Cross-References

- ▸First-Generation Antipsychotics
- ▸Olanzapine
- ▸Quetiapine
- ▸Risperidone
- ▸Schizophrenia
- ▸Second and Third Generation Antipsychotics
- ▸Ziprasidone

Clocapramine

Definition

Clocapramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class approved in Japan for the treatment of schizophrenia. It shows higher affinity for 5-HT2A- than for D2-receptors, but has more potent dopamine antagonist activity than carpipramine that belongs to the same class. Clocapramine can induce extrapyramidal motor side effects and insomnia, but it displays generally low toxicity.

Cross-References

- ▸Carpipramine
- ▸Extrapyramidal Motor Side Effects
- ▸First-Generation Antipsychotics
- ▸Schizophrenia

Clozapine

Definition

Clozapine was the first of the second generation of antipsychotic drugs. It has weak D2 receptor antagonist activity and also blocks D1 and D4 receptors as well as α-adrenoceptors, 5-HT2 receptors and muscarinic acetylcholine receptors. It is an effective anti-schizophrenia drug with little tendency to cause extrapyramidal motor disorders. Its main advantage is that it is effective in a substantial proportion of chronic schizophrenic patients who fail to respond to conventional antipsychotic medication. Its main disadvantage is its tendency to cause agranulocytosis in about 1% of patients and weekly monitoring of the white blood-cell count is mandatory. It has therefore become a third line antipsychotic.

Cross-References

▸Second- and third-generation antipsychotics
▸Schizophrenia

Cognitive Behavioral Therapy for People with Schizophrenia

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INTRODUCTION

Psychological approaches in the management of mental health problems have become established as routine treatment approaches for many disorders throughout the developed world. For some disorders, for example, anxiety and depressive disorders, psychological treatments can be the first line treatment. The psychological treatment of schizophrenia has received less attention in the literature, despite being applied to psychotic disorders for many years: early in the 19th century, Bleuler (▸5) advocated the use of psychotherapies with people with schizophrenia. Subsequently, in the first few decades of the twentieth century, research on psychological treatment of psychosis tended to be in the form of case study or case series reports. However, more recently, there has been a growing body of well carried out, controlled research describing and evaluating psychological treatments for psychosis suggesting that these have an important place in the management of such disorders. In addition, government legislation in many Western

countries is endorsing the use of psychological approaches for schizophrenia, for example, the National Institute of Clinical Effectiveness in the United Kingdom (2009), the United States PORT psychosocial treatment recommendations (2009)(Dixon et al, 2010) and the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders (2005) all make recommendations about the application of evidenced based psychological interventions for psychosis. As a result, this chapter will focus on those psychological approaches which are specifically recommended and for which there is a good evidence base, particularly individual CBT and Family interventions. Other approaches are covered elsewhere in this volume (see Chapters XX).

The development of psychological approaches in schizophrenia

Contemporary psychological interventions in psychosis have been influenced by a range of theoretical schools. Influences have come from psychoanalytic, cognitive and behavioural theory, but also from research into the psychopathological processes thought to be associated with schizophrenia. These influences have guided and contributed to the development of psychological approaches over the last 100 years. Psychoanalytical approaches to the treatment of psychosis have not been widely or systematically evaluated and there is little evidence that this type of approach can be helpful in the treatment of psychosis. Past reviewers of psychodynamic approaches for the treatment of psychosis have varied in their conclusions, with some authors suggesting that this type of approach has a place in the treatment of psychosis despite this conclusion being based on very little evidence (Huxley et al, ▸20). Other authors have concluded that psychodynamic psychotherapy is clearly not effective in schizophrenia and that it may possibly be unhelpful (Mueser and Berenbaum, ▸32). This, together with the paucity of evidence to suggest that psychodynamic psychotherapy is helpful in psychosis, have led some authors to conclude that there is no good rationale for large investments in evaluation of the approach given it is not likely to offer any advantages to other, well evaluated interventions that are already available (Tarrier, Barrowclough, Haddock and Wykes, ▸44).

There are a number of other psychological approaches, which have been explored although evidence in support of widespread adoption of the approaches is variable and, as yet, quite limited. These include approaches such as neuropsychological and cognitive remediation approaches; social skills training and contingency management approaches (see Haddock and Spaulding, ▸17 for a review of these approaches). Although these have been

widely applied clinically, the evidence in support of their effectiveness to date has been inconsistent and has led to caution by some professional and academic bodies in their recommendation. However, meta-analyses (e.g. McGurk et al, ▸28) suggest that the approaches have significant promise in improving outcomes in some areas. The cognitive remediation approach is described further in Chapter XX. In addition, other psychosocial approaches such as psychoeducation (see Rummel-Kluge and Kissling, ▸41 and Chapter XX) and compliance therapy (McIntosh et al, ▸29) also warrant investigation although trials, particularly for the latter, is smaller in number than for other interventions.

In contrast, individual cognitive behaviour therapy (CBT) and cognitive-behaviourally oriented family interventions (FI) have been well evaluated across a range of settings and cultures and have been shown to be efficacious in schizophrenia, with improvements in relapse rates, symptoms and functioning being observed.

Individual CBT for psychosis

This approach has a long history of use in the treatment of psychotic disorders, (see Beck, ▸5) and there has been a wealth of descriptions of interventions, usually focused on the remediation of particular psychotic symptoms i.e. hallucinations, delusions or negative symptoms. Early approaches were influenced more by the strictly behavioural psychology school, such as the use of contingency or reward approaches for reducing the occurrence of particular target behaviours (Nydegger, ▸35; Haynes and Geddy, ▸19), distraction procedures (Margo, Hemsley and Slade, ▸26; James, ▸21; Nelson et al, ▸33), thought stopping (Samaan, ▸42; Allen et al, ▸2) and the use of aversion therapy (Alford and Turner, ▸1). Whilst successful reductions in the occurrence of target behaviours were frequently reported using these approaches, there was little evaluation of this type of approach in larger controlled trials and little evidence that the approaches generalised across situations or people. These approaches highlighted researcher's and clinician's emphasis on the removal of psychotic symptoms and the notion that symptoms of psychosis were 'ununderstandable' phenomena and were therefore not likely to respond to reason or discussion. (Jaspers, ▸22). However, this notion of the 'ununderstandability' of psychotic symptoms has been much disputed in more recent years resulting in a greater understanding of the development and maintenance of psychotic symptoms. For example, the application of effective techniques to help individuals test out the reality of delusional beliefs (e.g. Chadwick and Lowe, ▸9) has demonstrated that, contrary to Jaspers earlier assertion, these beliefs do indeed respond to reason and are often understandable when considered in relation to the individual's beliefs and life experiences (Garety and Hems-

ley, ▸13). In addition, the growing interest in 'talking' therapies for the treatment of other disorders e.g. cognitive therapy for anxiety and depression, as well as the greater interest in understanding the nature of particular psychotic symptoms led to the development of psychological approaches that involved exploring and treating psychotic phenomena in one to one talking therapies. This heralded the development of cognitive-behavioural treatments for psychotic disorders which lent themselves well to evaluation in larger controlled trials of their effectiveness. CBT has been applied to all phases of the disorder i.e. acute and recent onset psychosis (Lewis et al, ▸25; Garety et al, 2007) and chronic and treatment resistant psychosis (Tarrier et al, ▸45; Sensky et al, ▸43). In addition, CBT has also been shown to be effective at reducing the transition to full-blown psychosis in those people experiencing pre-psychotic or high risk for psychosis states (Morrison et al, ▸30), and has been used with people who are experiencing co-morbid or dual disorders (Barrowclough et al, ▸3; Haddock et al, ▸15).

CBT is a one to one collaborative therapy. The approach assumes that the key problems of the client or patient develop and are maintained by cognitive (thoughts and beliefs), physiological (emotional reactions) and behavioural factors and that these factors can be modified using psychological means. Therapy typically lasts for between twelve and thirty sessions over a period of six to twelve months. Therapy sessions usually last for between 30 and 60 minutes although flexibility is required to ensure that the session length is suitably matched to the individual's concentration and other cognitive abilities. Therapy tends to consist of four main stages: 1) engagement and socialisation into the model, 2) assessment and formulation of key problems, 3) intervention strategies to reduce severity and distress, and 4) consolidation of the benefits obtained during therapy and strategies to enhance staying well. There is evidence that people with psychosis can engage in CBT regardless of the stage of illness, the acuteness of their symptoms or whether co-morbid disorders are present so no assumptions should be made about who would be most likely to engage.

Using information generated by collaborative exploration of the patient's problems and goals, a joint formulation of the individual's problems is agreed and appropriate targets or goals are prioritised for intervention collaboratively. Initial goals are likely to be focused on symptom reduction or the modification of coping strategies. Underlying core and long standing beliefs and behaviour patterns influencing current problems may to be tackled at a later stage in therapy, if appropriate, although they may be concurrently targeted.

Interventions usually cover the following areas: delusions, hallucinations, anxiety, depression, suicide, relapse prevention/keeping well, schemas, cop-

ing strategies, negative symptoms, medication compliance. However, this list is not exhaustive and interventions may vary considerably from individual to individual. Commonly used CBT techniques include: ongoing monitoring of key cognitions, behaviours and feelings, strategies to test out delusional or core beliefs (e.g. behavioural experiments), strategies to challenge and modify negative thoughts, strategies to enhance coping, developing helpful distraction strategies and motivational work to increase desire to take helpful medication. These approaches aim to reduce the distress and disruption of the individual's symptoms. They may not result in removal of the symptoms although this may occur for some people. Tools such as the Psychotic Symptom Rating Scales (Haddock et al, ▸16), the Maudsley Assessment of Delusions Scale (Buchanan et al, ▸8), the Beliefs about Voices Questionnaire-revised (Chadwick et al, ▸10) and the Service User Experience of Psychosis Scale (Haddock et al ▸18) can be useful to evaluate and monitor the impact of the intervention.

Evaluations of the effectiveness of individual CBT

Individual CBT has been subject to much evaluation in controlled and uncontrolled trials. Several trials have demonstrated the superiority of CBT (including 'treatment as usual' of anti-psychotic medication and care/case management approaches) over control treatments plus treatment as usual (See Rector and Beck, ▸39; Pfammatter et al, ▸37; Jones et al, ▸23; Wykes et al, ▸47 for reviews). Trials have varied in the methodology used, the samples included and the type and 'dose' of CBT applied leading to difficulties in clearly elucidating what the essential aspects of intervention are. Nevertheless, Wykes et al (▸47), in their recent meta-analysis, concluded that CBT consistently showed superiority over control treatments, with an overall mean weighted effect size taken from 33 studies of 0.4. However, the effect size of the treatments evaluated in the trials reviewed decreased when the quality of the methodology employed by the researchers carrying out the studies increased.

Cognitive-behaviourally oriented family interventions for psychosis

A substantial amount of research has demonstrated that providing family interventions can significantly reduce relapse rates of people with psychosis over follow-up periods (Pfammatter et al, ▸37; Pharoah et al, ▸38). Family interventions are based on the assumption that a stressful interpersonal environment in which an individual lives can exacerbate psychotic symptoms and lead to premature or more frequent relapse of illness. This type of stressful environment is often one referred to has being high in 'Expressed Emotion'. This term was first described in relation to families by Brown and

colleagues (Brown et al, ▸7) following observations that people with schizophrenia who were discharged from hospital to live with parents or close family fared worse than those who lived alone or in hostel accommodation. Brown and colleagues developed a measure of 'expressed emotion' (EE) that could be used to assess the emotional climate in an individual's home environment. It is characterised as one in which the interpersonal environment is high in critical comments, hostility and emotional over involvement. Research showed that those individuals living in environments scoring high on a measure of high EE resulted in significantly higher relapse rates for the individual with schizophrenia than those in low EE environments (Brown et al, ▸7; Vaughn and Leff, ▸46). This finding has now been replicated many times in different settings and in different populations.

Family intervention treatment programmes

A number of different family approaches have been evaluated (see Pharoah et al, ▸38 for review) and although they may differ in the techniques employed they tend to be cognitive-behavioural in their underpinning therapeutic model and have major aspects in common. They usually focus on attempting to improve the interpersonal environment by providing the following key elements: 1) assessment and problem formulation (similar to that involved in individual CBT) in order to identify key problem areas 2) information about the nature of the illness, its prognosis and treatment and 3) intervention and problem solving strategies to address areas of conflict and concern, goal setting to improve social and interpersonal functioning of all family members.

Family interventions can involve close family members and carers and may also be effective with staff groups for people living in inpatient environments (Oliver and Kuipers, ▸36). Interventions are often delivered with single families although interventions delivered to groups of families simultaneously have also been shown to be effective (McFarlane et al, ▸27). There is no limit to the numbers of family members that can be engaged in the approach although for practical reasons it is often limited to those living in closest contact with the individual such as parents, partners, brothers and sisters. Family interventions typically last for between six and twelve months, with sessions weekly or fortnightly. The meetings are flexible with some sessions taking place as a family group with the individual, some taking place with relatives alone and others with the individual sufferer themselves. The exact nature of the sessions will depend on what is collaboratively agreed between all parties during assessment and formulation sessions. As the approach is collaborative, agreement from all parties as to what takes place is important within the confines of each stage.

Structured interviews and questionnaires can be used to assist with this process, for example, The Relative's Assessment Interview and Knowledge about Schizophrenia Interview (Barrowclough and Tarrier, ▸4) and General Health Questionnaire (Goldberg, ▸14).

Information about the nature of the illness, its prognosis and treatment is often provided early on in treatment. Helping relatives and sufferers to gain correct information and understanding about the nature of the psychotic illness, the causes, prognosis and the treatment is important and can help correct erroneous beliefs that may have been driving relative's behaviour and can help with the discovery and implementation of more helpful behaviours. It can also reduce the distress and allay any fears that have arisen from mythical or media sources. It is helpful if information provision is delivered in a way that is 'tailored' to the needs of the family members.

Intervention strategies should address key areas of conflict and concern, involve setting individual and family goals and improve functioning. The specific intervention strategies will depend on the needs of the individual patient and their family; however, some common elements are usually involved. For example, most interventions will provide strategies to assist patients and carers to set realistic and achievable goals and provide assistance in achieving these with the intention of improving functioning of family members and patients. Some approaches will include strategies to assist with managing unpleasant affect, distress and symptoms. Action plans involving all family members are often used to assist relatives to monitor and detect early signs of relapse and to provide a plan of action should any family member become aware of early signs of relapse. The family intervention may also be delivered in tandem with individual CBT for family members and patients where necessary to deal with any individual problems (see Barrowclough and Tarrier, ▸3; Falloon, ▸12; Mueser & Glynn, ▸31; Kuipers, Leff and Lam, ▸24 for detailed descriptions of interventions).

Effectiveness of family interventions

Family interventions have been rigorously evaluated indicating consistent superiority of the approach compared to treatment as usual on relapse rates (Pfammatter et al, ▸37) with replications in many parts of the world including Eastern and developing countries (Xiong et al, ▸48). Recent meta-analyses have varied in their conclusions however, reviews consistently conclude that family interventions can significantly reduce relapse. The Cochrane systematic review of family interventions in schizophrenia (Pharoah et al, ▸38) concluded that family interventions can reduce the frequency of relapse, reduce hospital admission and increase adherence to medication.

Conclusions

Psychological treatments, particularly CBT, are important in the treatment of psychosis and offer significant benefits in a range of areas, particularly, in reducing relapse, hospital admission, symptom severity and distress and improving cognitive functioning and performance. In addition, wider benefits for the individual and services may be observed, such as reduced violence and aggression, improvements in medication adherence, reductions in substance use, reduced suicide and benefits for relatives and carers. Further research is necessary to elucidate the exact ingredients for therapy and what treatment is best suited to which individual.

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Cognitive Impairment

Synonyms

Cognitive deficit
Neurocognitive dysfunction

Definition

C *ognitive impairment* is considered a core feature of *schizophrenia* that is related to the daily functioning of patients. On average, *cognitive impairment* in schizophrenia is severe to moderately severe compared with healthy controls. *Cognitive impairment* is not state-related and is not specific to subtypes of the illness. It includes problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. These deficits can also serve as an endophenotype for the illness and are considered a reasonable treatment target in individuals with schizophrenia.

Cross-References

▸Schizophrenia

Cognitive Remediation in Schizophrenia Patients

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Synonyms

Cognitive rehabilitation

Definition

Cognitive remediation for schizophrenia is a behavioral intervention consisting of training activities which aim to target a range of cognitive impairments, including deficits in attention, memory, executive functioning, social cognition, and theory of mind, with the ultimate intent of improving functional outcome.

Significance of Cognitive Impairment in Schizophrenia

Cognitive impairment is a core symptom of schizophrenia that is evident at first episode of psychosis and persistent but stable, throughout the course of illness. Cognitive deficits are most pronounced in the areas of attention, verbal memory, processing speed, and executive functioning, with magnitude of deficit between one and two standard deviations below the mean for healthy individuals. While 70–80 of people with schizophrenia show cognitive impairments relative to the general population, close to 100 have cognitive deficits relative to their own premorbid ability level. The status of neurocognition and social cognition has been shown to have prognostic value, predicting whether a person with schizophrenia will be able to meet functional goals (Green, ▸1). Functional goals may include those related to symptom management and participation in psychosocial rehabilitation programs, and to those related to community integration, including functioning in social, vocational, and educational domains. Cognitive deficits add significantly to illness burden and thus have increasingly been the focus of developing interventions over the last 20 years.

Common Principles of Cognitive Remediation for Schizophrenia

Given the empirical foundation upon which the rationale for cognitive remediation for schizophrenia is based, programs of cognitive remediation are grounded in theory and empirical evidence. The philosophical and practical underpinnings of cognitive remediation for schizophrenia are based upon the foundational platform of *psychiatric rehabilitation*. The psychiatric rehabilitation model differs from a traditional medical model in treating psychiatric illness in that, instead of focusing on eliminating symptoms, rehabilitation methods aim to decrease level of disability, promote adaptation, and thereby improve psychosocial functioning (Silverstein, ▸9). Accordingly, there are two central tenets underlying all treatments defined as cognitive remediation for people with schizophrenia:

1) Cognition can be rehabilitated through behavioral learning based interventions that promote neuropsychological and social cognitive skill performance.
2) Through targeting specific areas of dysfunction, improvements in cognitive performance are translated to produce changes in real-world functions.

Specific methods of treating cognition in schizophrenia are founded upon cognitive psychology and neuropsychology. Additionally, cognitive remediation is inspired by methods of rehabilitation with neurologically im-

paired populations and is often informed by methods of learning enhancement, developed within the fields of educational and clinical psychology. Cognitive remediation for schizophrenia is predicated upon evidence for *neuroplasticity* - that neuroanatomical connections may be strengthened and/or repaired, yielding changes in neuropsychological abilities. Cognitive remediation aims to restore cognitive skills that have been adversely affected by illness processes. Drill and practice exercises are typically employed, most often using computerized cognitive training exercises, but also may be presented as paper-and-pencil or verbal tasks. Compensatory techniques may also be used to augment restorative approaches. Compensatory techniques teach the use of strategies to offset cognitive deficits by relying on more intact cognitive and psychological functions. In as much as cognitive remediation is a training activity, it relies on principles of learning, which include the role of motivation in the learning process and outcomes.

Two theoretical approaches drive the structure and format of restorative remediation techniques. In "bottom-up" programs, exercises gradually progress through a hierarchy of abilities from the so-called elementary cognitive domains of basic information processing, (e.g. attention, reaction time and working memory) to the more complex abilities known as *executive functioning*, which include abstract reasoning, sequencing and problem-solving. In "top-down" programs, exercises that target executive functioning are initiated from the outset, according to the notion that basic foundation skills are being engaged and trained simultaneously along with more complex abilities. The role of engaging *metacognition* (i.e. "thinking about one's thinking") in cognitive remediation has gained increasing emphasis, as employing analytical thinking skills not only exercises specific neurocognitive abilities, but also increases awareness of cognitive processes in relation to real-world functions.

Whether utilizing a bottom-up or top-down approach, training activities aim to yield changes in cognition which are generalizable to skills applicable to a range of functional domains including independent living, social, education, and vocational functioning. Training activities may be selected to target specific cognitive abilities or areas of functioning in the context of an individual's personal strengths, weaknesses, and one's unique rehabilitation goals. Thus a fundamental element of cognitive remediation for schizophrenia is that a treatment plan may be tailored to suit the specific needs of the individual. To some extent this can be accomplished, within the context of computer-based cognitive remediation, by software programs that use task performance to automatically calculate the appropriate menu of activities or adjust in level of difficulty. However increasingly it is recognized

that cognitive remediation is most effective when conducted in the context of a broader psychosocial rehabilitation program that explicitly links cognitive outcomes to recovery goals. Consequently, more cognitive remediation programs are starting to pair specific cognitive enhancing activities with vocational training, social skills and independent living skills training. *Bridging groups*, which are verbal groups that include explicit discussion of the link between cognitive exercises and everyday functioning, are also used in conjunction with cognitive training exercises to provide the broader rehabilitative context for treating cognition.

Social cognition is a specific domain of cognitive functioning that has emerged as playing a significant role in influencing psychosocial functioning in schizophrenia. There is considerable interest in the development and dissemination of skills-based interventions that specifically target impairments in social cognitive processing. Thus cognitive remediation programs increasingly include exercises that address the mental operations that underlie social interactions, such as perceiving, interpreting and generating responses to social stimuli. Specific social information processing skills, including affect recognition, social perception, attributional bias, and theory of mind are integral to generating appropriate responses within a social context, and are often targeted in cognitive remediation programs for people with schizophrenia. Intervention techniques focused on the cognitive skills underlying social processes are sometimes combined with *social skills training*, which focuses on the expressive and behavioral elements of social functioning; social skills training bridges social cognitive treatment activities to pertinent real-world contexts. Pairing training techniques that target social information processing with those that target social skills ostensibly facilitates the generalization of social cognitive gains to maximally impact functional outcomes (Grynszpan et al., ▸2).

The remediation methods employed and functional context in which cognitive remediation is conducted are guided by theory and empirical data, but are adaptable to suit the needs of the population with whom the program is implemented. Cognitive remediation can be conducted individually or in groups, with sessions occurring on average twice a week for three months. Some programs may have greater intensity (i.e. more frequent sessions) and longer duration (i.e. up to two years) depending on the treatment setting, goals and/or severity of deficits. The relative efficacy of different dosing schedules, and benefit of booster sessions after training ends remains unresolved. Cognitive remediation is conducted by mental health clinicians who receive specific training to do this intervention.

Empirical Support

Empirical support for cognitive remediation in schizophrenia is documented by a wealth of published randomized controlled trials which together have studied over 1500 patients. This literature has been reviewed in several meta-analytic studies, which while differing in focus, have consistently found moderate effect sizes (Grynszpan et al., ▸2; Krabbendam and Aleman ▸3; McGurk et al. ▸5; Twamley et al. ▸10) on the impact on neurocognitive performance, social cognition and functional outcome. Effects on cognitive skill performance are durable on average 8 months after the therapies are withdrawn, with effect sizes in the moderate range, particularly in terms of executive ability, working memory, and verbal memory (Grynszpan et al., ▸2; McGurk et al., ▸5). Importantly, neurocognitive gains have been linked to improvements in obtaining and working in competitive jobs, the quality of interpersonal relationships, social behaviors and problem-solving skills needed for independent living (McGurk et al., ▸5).

In considering the broad range of symptoms associated with schizophrenia, cognitive remediation is relatively specific in improving the neuropsychological and social cognitive abilities targeted. Cognitive remediation is not intended to target psychiatric symptoms, although data suggest that some generalization of treatment effects may be evident with effect sizes for psychiatric symptoms in the small range (0.28; McGurk et al., ▸5). Psychiatric symptom improvement might be considered secondary to neurocognitive change, perhaps due to improvement in functioning, self-perception, and mood.

Variables Affecting Treatment Outcomes

Several variables have been found to moderate the effects of cognitive remediation on neurocognition, social cognition and psychosocial outcome. Learning context accounts for a significant amount of variability in the magnitude of effect. Empirical data suggest an influential role of:

1) Program setting
2) Instructional techniques
3) Client factors

In general, there is more variability in the effect on psychosocial outcomes than cognitive outcomes. Stronger effects are observed for improved psychosocial functioning when cognitive remediation is embedded within a psychiatric rehabilitation program, suggesting that the gains in cognitive functioning do not automatically generalize to functional gains. Data indicate that there is a significant difference in the magnitude of effect size on psychosocial functioning between cognitive remediation programs that

stand alone (0.05) versus those that are integrated (0.47) with other behavioral recovery-based treatments (McGurk et al., ▸5). When cognitive remediation is tied to a larger context, such as individual recovery goals, treatment engagement may be enhanced, and improved cognitive ability may enable some people to participate in and thus make greater gains from psychosocial rehabilitation. Cognitive remediation programs may also capitalize on specific instructional techniques and the social environment to offset the negative impact of low baseline motivation common to people with schizophrenia. Use of strategy coaching, which teaches methods to enhance recall and facilitate use of problem-solving skills during training activities, may increase the salience of cognitive skills and help clients to bridge the treatment environment to real-world functioning. For example, whereas drill and practice instructional techniques yield effects in the small range (0.24), combining drill and practice with strategy coaching (0.62) significantly augments psychosocial outcomes for cognitive remediation (McGurk et al., ▸5).

A social learning context in which the instructor provides individualized attention, guidance, and opportunities for choice of learning activities rather than administering a generic program of learning, may promote a positive treatment environment, foster self-determination, and support treatment engagement. Some interventions capitalize on the contextualization of learning activities to enrich the instructional content of remediation sessions and to enhance intrinsic motivation in people with schizophrenia (Medalia et al., ▸7). Contextualization refers to the presentation of learning activities in reference to real-world scenarios, illustrative of the practical utility of cognitive skills. By personalizing a cognitive remediation program, contextualizing training activities to bridge treatment to everyday life, and supporting a sense of self-efficacy, engagement in the learning process may be facilitated and functional outcomes may be augmented.

Aspects of the treatment environment interact with certain client characteristics, which must be identified in order to further promote learning and enhancement of cognitive gains. Type and extent of baseline cognitive disability has been shown to impact degree of cognitive improvement, thereby suggesting these are client factors to consider when developing a personalized treatment plan and implementing cognitive remediation strategies. More globally impaired patients may have greater difficulty generalizing gains from training tasks to novel or untrained tasks, and patients with more attention impairment at baseline may require specific strategies to benefit from cognitive remediation (Medalia and Choi, ▸6). In contrast, there is little evidence to suggest that socio-demographic characteristics (e.g. gen-

der, age, ethnicity) significantly predict whether an individual will benefit from cognitive remediation.

Empirical data support the notion that degree of engagement in cognitive remediation impacts magnitude of improvement. Although cognitive remediation outcomes do not appear to vary systematically as a function of program duration (Grynszpan et al., 2010; McGurk et al., ▸5), more consistent attendance to cognitive remediation sessions appears to have a positive impact such that people who miss sessions benefit less (Medalia & Choi, ▸6). Clients' motivation to participate in cognitive remediation on a consistent basis, or ability to adequately attend to training activities within sessions may be influenced by the degree or type of baseline impairment, thus ultimately impacting the degree to which cognitive remediation is beneficial. Additional data indicate that perceived self-competency and the perceived utility value of learning activities significantly predict magnitude of neurocognitive change (Medalia and Choi, ▸6). These data suggest that client factors that influence *intrinsic motivation* for cognitive remediation appear to promote treatment engagement, enhance learning, and thus have a positive impact on treatment outcomes. Overall, promoting treatment engagement through moderating program setting, instructional techniques and attention to pertinent client factors is key in effectively targeting cognition and optimally improving functional outcomes for people with schizophrenia.

The Current State of Cognitive Remediation for Schizophrenia

Programs of cognitive remediation for schizophrenia are disseminated and are currently implemented around the world. Cognitive remediation is typically provided in community-based programs and long-term care settings and, as data suggest, while it has consistent robust impact on cognitive functioning regardless of how it is implemented, it is most effective at improving community outcome when provided in the broader context of psychosocial rehabilitation. A broad range of neuropsychological deficits and social cognitive functions may be targeted, although cognitive remediation for schizophrenia is increasingly focused on targeting those deficits which contribute most significantly to social dysfunction and community outcome. Current approaches incorporate training activities to strengthen both lower and higher order cognitive processes, utilizing paper-and-pencil, computer, and/or skills-based intervention strategies.

Recent attention has turned to incorporating theories of motivation into the understanding and treatment of cognitive dysfunction in schizophrenia. The learning context in and by which cognitive remediation is implemented is relevant to the strength of the effect of treatment via treatment adherence

and magnitude of learning. Strategies to facilitate motivation and to facilitate generalization of neurocognitive skills to functional skills may be further elucidated by ongoing research. Enhancing intrinsic motivation to engage in cognitive remediation may promote greater adherence, deeper processing during training tasks, and greater application of what is learned to real-world functions. The ultimate goal of cognitive remediation for schizophrenia is to help individuals attain personal rehabilitation goals to support their success in the community.

Cross-References

▸Cognitive Impairment
▸Schizophrenia

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Compliance

Definition

Compliance has been defined as "the extent to which the patient's behavior coincides with medical or health advice. It is also been defined as "the ratio between an observed treatment behavior and given treatment standards".

Cross-References

- Antipsychotic Drugs
- Family Based Approaches for Schizophrenia Patients
- Psychoeducation in the Management of Schizophrenia
- Second and Third Generation Antipsychotics

CUtLASS

Synonyms

Cost utility of the latest antipsychotic drugs in schizophrenia study

Definition

Study comparing an impact of the treatment with First Generation Antipsychotics and Second Generation Antipsychotics on quality of life. The main result is a lack of significant difference in this respect. The study also compares efficacy of predominately sulpiride with the SGA in the treatment of schizophrenia. In general, sulpiride was as effective and well tolerated as the SGA.

Cross-References

- First-Generation Antipsychotics
- Schizophrenia
- Sulpiride

Delayed Onset of Drug Effects

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Synonyms

Delayed onset of action

Definition

According to the theory of delayed onset of action, the effects of antipsychotic or antidepressant drugs occur only after a delay of several weeks.

Current Concepts and State of Knowledge

The Concept

This chapter deals with the "delayed onset of action" hypothesis of antipsychotic and antidepressant drugs. This old theory states that antipsychotic or antidepressant drugs do not start to improve the symptoms immediately after administration, but that it rather takes several weeks until their effect sets in. It is shown that the "delayed onset of action" hypothesis is a myth and that the onset of action is early if not immediate. This article focuses on the evidence of ▸antipsychotic drugs, but similar findings on antidepressants are briefly summarized at the end.

Historical Background

This theory probably emerged in the early 1970s, but there is no single author who could be quoted as its inventor and the statements in early textbooks were actually quite vague. For example, in 1969, Klein and Davis wrote in their seminal textbook: "Figs. 2–5 show that improvement takes place over long periods of time. In order to obtain maximum clinical effect, the patient must be treated with an adequate (antipsychotic) drug dose for an adequate time period" (Klein and Davis ▸6). It then seems that the explanation of the effects of antipsychotic drugs by the depolarization block theory lent support to a delay of onset. The depolarization block theory was based on the studies on rats showing that antidopaminergic treatment leads to inactivation of dopamine firing and that it takes 3 weeks until the inactivation is in effect. This delay in the occurrence of the biological marker was thought to coincide with and explain the delay of onset of antipsychotic drug effects (Agid et al. ▸1). Although the delay of onset of antipsychotic drug action had never been validated in clinical trials, it became widely

recognized and was codified in many psychiatric textbooks (e.g., Gelder et al. ▸3).

Refutation of the Delay of Onset of Action Hypothesis

Although the assumed delay of onset was a key concept in the mechanisms of action of antipsychotic drugs, it has only recently been systematically investigated. Two large, independent meta-analyses clearly refuted the theory (Agid et al. ▸1; Leucht et al. ▸7). A pivotal meta-analysis by Agid et al. (▸1), based on 47 double-blind studies including 7,450 patients with schizophrenia, showed that the reduction of the overall positive symptoms in the first 2 weeks was greater than that in the subsequent 2 weeks. Leucht et al. (▸7) confirmed this finding using 1,708 original patient data from randomized controlled trials. In addition, they extended the analysis to 1 year and found that the largest part (68%) of the antipsychotic drug effect occurred in the first 4 weeks of treatment. Several subsequent analyses showed that the effects of antipsychotic drugs can be separated from that of placebo as early as within 24 h after the initiation of treatment (e.g., Kapur et al. ▸4). In summary, these analyses clearly showed that the "delay of onset" was a myth, but that the onset of antipsychotic drug action rather sets in early.

Why Has the Delay of Onset Hypothesis Prevailed for such a Long Time?

There is an important distinction between a delay of "onset" and a delay of "development of full antipsychotic effects". While the recent studies have clearly refuted the concept of a delay of *onset* of drug action, it is very clear that it usually takes several weeks or even months until an antipsychotic drug develops its *full* effects or until a patient is in remission. It is likely that a confusion of these two concepts fueled the misunderstanding.

Consequences for the Understanding of the Mechanism of Action of Antipsychotic Drugs

The rejection of the delay of onset of action hypothesis has major implications for the explanation of the mechanism of action of antipsychotic drugs. The delay of onset of action suggested that the well-known effects of antipsychotic drugs on ▸dopamine receptors are not directly responsible for the therapeutic effect, but rather postsynaptic mechanisms. As it is now clear that antipsychotic drugs start working without a delay, it is more likely that the blockade of dopamine receptors is also key in mediating the clinical response.

Does Early Improvement Predict Later Response?

The new "early onset of antipsychotic drug action" hypothesis also has major clinical implications. Due to a belief in the former theory of delay of onset, the treatment guidelines recommended to keep the patients for up to 6–8 weeks on the same drug before it should be considered ineffective and switched. As it is now clear that antipsychotic drugs can exert important effects in the first few weeks, it is possible that the degree of early improvement in 1 or 2 weeks predicts later treatment success. Already in the 1980s and 1990s, several studies showed that the degree of symptom reduction in 1 or 2 weeks strongly correlated with the degree of response after 4–8 weeks (e.g., Bartko et al. ▸2). While these studies suggested that the degree of early improvement may be used as a predictor of later response, they were small and only correlational in design, that is, they did not come up with cutoffs of early improvement that could serve as predictors for later response or remission. A reliable measure such as a diagnostic test with high specificity, sensitivity, positive and negative predictive values is needed. Such a test would indicate whether a patient is an early improver or an early nonimprover, and would further predict whether a patient would develop a full response at later stages. Stimulated by the meta-analysis of Agid et al. (▸1) several recent investigations have tried to develop such a test and usually based it on a minimum percentage reduction of the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) total score in 1 or 2 weeks (e.g., Leucht et al. ▸8). Although these analyses differed in populations (e.g., patients in registrational trials versus naturalistic settings), study duration (4–12 weeks), or definition of response (e.g., at least 20 or 50% BPRS/PANSS reduction or remission), they by and large found that minimal improvement (e.g., less than 25% BPRS/PANSS total reduction from baseline) in 1–2 weeks could serve as a predictor nonresponse at later time points (4–12 weeks).

In the Case of Nonresponse – Should Antipsychotic Drugs Be Switched Early On?

The fact that early improvement is a good predictor of later response suggests that the antipsychotic drug of early nonimprovers should be switched. But is this really true? It could also be that early nonimprovers have a poor outcome, irrespective of the antipsychotic drug used. It is necessary to find out whether an early switch to the antipsychotic drug really improves outcome from randomized studies in which early nonresponders are either switched to another antipsychotic or are kept on the same one. The first large double-blind study of this kind has been completed and it indeed showed that those patients who had not responded to 2-week treatment with ▸risperidone were more likely to respond if they were switched to

▸olanzapine than if they stayed on risperidone for another 10 weeks (Kinon et al. ▸5). However, the gain was relatively small and the early nonimprovers never caught up with the early improvers, even if they were switched to olanzapine. As olanzapine and risperidone are both atypical antipsychotic drugs with similar receptor-binding profiles, studies on drugs with more different receptor-binding profiles are now needed. Such studies could also investigate other strategies, for example, an early switch to the most efficacious antipsychotic drug ▸clozapine, high dose strategies, or augmentation with other psychotropic compounds.

Delay of Onset of Antidepressants

As mentioned in the beginning of this article, the treatment of schizophrenia with antipsychotic drugs was used as an example, but there was also a delay of onset hypothesis in the treatment of depression which has recently been refuted. Taylor et al. (▸10) published a meta-analysis of 28 randomized controlled trials including 5,872 participants and found that the effects of selective serotonin reuptake inhibitors (SSRIs) separated from those of placebo by the end of the first week of use and the rate of improvement decreased in the following 5 weeks. Szegedi et al. (▸9) demonstrated in a large database of 6,562 patients from 41 randomized antidepressant drug trials that early improvement predicted later response with sufficiently good test values (Taylor et al. ▸10; Szedegi et al. ▸9).

Cross-References

▸Atypical Antipsychotic Drugs
▸Dopamine
▸Schizophrenia
▸Second and Third Generation Antipsychotics

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Delusional Disorder

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Synonyms

Capgras syndrome
De Clerambault's syndrome
Delusional halitosis
Delusions of infestation
Delusion of interpretation
Delusional parasitosis
Dermatophobia
Erotomania (also known as De Clerambault's syndrome)
Ekbom's Syndrome
Inventors delusion
Inventors' psychosis or "inventors" delusion (in German: "Erfinderwahn" or "Erfindungswahn")
Megalomania; Michael Kohlhaas' syndrome
Koro

Othello syndrome
Paranoid delusions
Paranoid psychosis
Paranoia
Persecutory delusions
Querulous paranoia
Sensitive delusion of reference
Psychose passionelle.

Definition

Paranoia/paranoid psychosis was renamed by Winokur (▸9) as delusional disorder. Different forms of the disorder have been well described since the early nineteenth century (Grover et al. ▸4). Delusional disorder is characterized by the presence of one or more delusions, which are not bizarre. These delusions may occur in real life and last at least 1 month according to the fourth Edition of the Diagnostic and Statistic Manual (DSM-IV) of Mental Disorders and at least 3 month according to the Tenth Revision of International Classification of Diseases and Related Health Problems (ICD-10) (American Psychiatric Association ▸1). Bizarre and nonbizarre delusions may be difficult to differentiate. However, delusions of control, thought broadcasting, thought insertion, and thought withdrawal are described as bizarre delusions, while persecutory, somatic, grandiose, and religious delusions, as well as most delusions of jealousy are described as nonbizarre. Examples of nonbizarre delusions include false beliefs of being followed or loved, of having special abilities, power or wealth, etc.
Delusional disorder can be diagnosed if diagnostic criteria for schizophrenic disorder have never been met and organic mental disorders and psychoactive/drug-induced psychotic disorders can be excluded. Delusions are the leading symptoms of this disorder even if some hallucinations are present. Patients suffering from delusional disorder may have well-preserved social and work functions in spite of complete or almost complete lack of insight.

Role of Pharmacotherapy

Phenomenology of Delusional Disorders

Delusional disorder is a rare condition, the lifetime morbidity risk is estimated to be less than 0.2%, the annual incidence is 1–3 new cases per 100,000 persons. The types of delusional disorder are defined based on the predominant delusional theme (Sadock and Sadock ▸7). They are:
Erotomanic Type: having a delusion of a secret lover; the "lover" is often a famous person, a celebrity. The person with this type of delusional disorder may or may not contact the person, who is object of the delusion. The char-

acteristics of this disorder have been excellently described by de Clerambault (▸2): "Fundamental postulate: *It is the Object who began it and who loves the most or is the only one to love*. (N.B.: Object usually of high birth, classic notion". Some of the derived themes are: "The Object cannot achieve happiness without the suitor…. The Object is free. His marriage is invalid".

Grandiose Type: having delusion/s of one's own extreme greatness, goodness, knowledge, power, and/or wealth, having special relationship to famous persons, having famous ancestors.

Jealous Type: having a delusion of unfaithfulness of the spouse/sexual partner. It includes accusations of infidelity/testing the fidelity, searches for evidence of infidelity, questioning/interrogation of the partner, and also stalking. As Shakespeare described in his play "Othello", delusions of jealousy can be very dangerous and result in homicide and suicide.

Persecutory Type: having a delusion of persecution – it is one of the most known delusional disorders. Being followed by the police, Mafia, FBI, KGB, etc., are frequent contents of persecutory delusions.

Somatic Type: having a delusion of somatic disorder/pathology, such as Ekbom syndrome (delusional parasitosis), which is characterized by delusions about the skin being infected (e.g., the skin is infected with parasites, "small bugs"). Some patients with Ekbom syndrome may have unusual delusions, which may qualify for bizarre delusions, e.g., claiming that invisible "small houses" are in the skin. Another example is koro, which is characterized by delusions of penis shrinkage and retraction into the body or a delusion that the genitals have been stolen. Koro has been more frequently reported from Asia, but also described internationally for hundreds of years. Somatic defects may lead these patients to plastic surgeons. Some patients claim having a specific disease, e.g., AIDS in spite of the fact having negative laboratory findings. The delusions (e.g., the patient may claim that the laboratory values were falsified) differentiate it from hypochondriasis. Current diagnostic systems classify individuals with dysmorphic delusions into two groups: delusional body dysmorphic disorder and delusional disorder, somatic type. The differentiation may be difficult: a good example is the delusional complaint about ugliness.

Mixed Type: persons have more than one delusional theme.

Religious delusions are not included in the diagnostic systems as a type of delusional disorder, but they are frequent in some parts of the world (e.g., in the city of Jerusalem) and their differential diagnosis may be rather difficult. It can be part of ▸schizophrenia, manic episode of bipolar disorder, delusional disorder, or of other psychotic disorder, however it may be a shared belief of a religious community. The consensus of the given com-

munity can help in understanding the difference between their religious beliefs, practices, and delusions.

Querulous paranoia has rarely been reported from some parts of the world (e.g., China), which may have been related to the underdetecting and underreporting of this disorder. Querulous paranoia has practically disappeared from the psychiatric literature; however, it seems to be flourishing in modern complaints organizations and the courts (Lester et al. ▸6). Thus, social and cultural factors have a major influence on the detection and diagnosis of some forms of delusional disorders.

Delusion of reference is often part of the above mentioned types of delusional disorder. Delusion of reference is characterized by false beliefs about remarks, events, or objects unrelated to the person by giving them person related meaning and significance. Mistrust and hypersensitive personality are typical features of the syndrome.

Cotard delusion or Cotard's syndrome, is also known as nihilistic or negation delusion. Patients may claim having no arms or legs, in severe cases may even deny to exist. This delusion is part of other psychiatric disorders, such as schizophrenia or most often of severe (melancholic) depression.

Genealogical delusions are characterized by false beliefs about the descent of a person through an aristocratic or famous ancestral line. Genealogical delusions are part of other psychiatric disorders and interestingly the theme of the delusions changes over time, e.g., nowadays no patient claims being related to the Habsburg emperors.

Shared paranoid disorder (also known as shared psychotic disorder, induced psychotic disorder, folie á deux, and double insanity) is characterized by the transfer of delusions from one person to the other. They "share" the same false beliefs. Persons involved are close to each other, mostly have lived together for a long time. Shared paranoid disorder is considered to be a separate psychiatric disorder; it is not included in the group of delusional disorders.

The aetiology of delusional disorder is not known. Most probably it includes different conditions which share the presence of nonbizarre delusions; however, the available literature indicates substantial heterogeneity of this diagnostic category. Neurobiological and neuropsychological correlates of delusions suggest dysfunctions of the prefrontal, limbic, and subcortical regions, however further studies are needed (Kunert et al. ▸5). Toxic and organic origin of the disorder has been repeatedly described in the literature. Delusions of patients with organic brain syndromes are looser and simpler, and often temporary. Patients with complex and systematized delusions showed only slight cognitive impairment, which may indicate that largely

intact cognitive functions are an important prerequisite for elaborate delusional processing (Kunert et al. ▸5).
The female:male ratio in delusional disorder is around 3:1. Recent studies found only a slightly increased prevalence in females, and could not confirm the 3:1 ratio. The grandiose type affects almost only men, while the erotomanic type is more frequent in women. The most frequently encountered type is the persecutory type, followed by the somatic type and jealous type. The age at onset is around 40 years, however, there are differences described according to the type of delusional disorder, the oldest age at onset being associated with the persecutory type, and the youngest with the somatic type (Yamada et al. ▸10). The onset is often insidious. Key experiences may facilitate the development of this disorder. Delusions may have an interpretative character related to the key experience – in this case the disorder starts with a real event/sensation followed by delusional interpretation and an uncontrollable drive to relate everything to himself. Other delusions, (e.g., most erotomanic delusions) are autonomous, not related to any experience.

Treatment

Delusional disorders are difficult to treat; to our knowledge no drug has been approved for its treatment until April 2009, when this chapter was written. Publications about the pharmacological treatment of delusional disorders are focusing on the use, actually on the off-label use, of ▸antipsychotic drugs. The off-label status of antipsychotics in delusional disorders is a very severe limitation in prescribing them with this indication. Before considering pharmacotherapy the diagnosis has to be confirmed, other disorders and conditions that may cause delusions have to be excluded, such as schizophrenic disorder and organic brain syndromes. It may be difficult to differentiate between delusions/paranoid development and inappropriately rigid, unwavering demands to receive that which is due to us, whether such action is practical or not and leads to catastrophic consequences or not (e.g., the case of Michael Kohlhaas as described in the novel of Heinrich von Kleist).
The treating personnel need some training in psychiatry. Two major problems may arise with untrained staff members: (1) arguing with the patient about the delusions, trying to convince him about the unreality and senselessness of his delusions; (2) submission to the delusions, deal with delusions as with part of reality. In the first case the patient may leave the treatment immediately, in the second case the patient sooner or later will realize that the physician (or other staff member) is lying. While most patients with delusional disorder are treated as outpatients, in case of danger to himself or to others (see Othello syndrome above) urgent and even involuntary hospitalization is indicated. Due to lack of insight, which is a core feature

of delusional disorder, patients do not seek psychiatric treatment. With somatic type of delusional disorder patients may turn to other specialists, such as dermatologists in the case of Ekbom syndrome, which gives the opportunity to provide these patients with appropriate treatment. Well-organized consultation – liaison psychiatric services could improve psychiatric treatment, including the treatment of these patients.

Since we are dealing with a rare disorder, which even if diagnosed is still rarely treated and difficult to treat and there is no approved drug for its treatment, it is not surprising that there is a dearth of strong evidence-based data. However, the available data support the usefulness of both first and second generation antipsychotic drugs (Smith and Buckley ▸8) antipsychotic drugs, ▸first-generation antipsychotics, and ▸second and third generation antipsychotics. Early publications on antipsychotic treatment of delusional disorders focused on the efficacy of ▸pimozide, a first generation antipsychotic drug. This finding supported the ▸dopamine hypothesis of delusions. The use of pimozide significantly decreased partly because of the increasing use of second generation antipsychotics and partly because of safety concerns (ECG changes) with pimozide. Among the second generation antipsychotics, most experience in the treatment of delusional disorders is with ▸risperidone and ▸olanzapine (Freudenmann and Lepping ▸3). The reported full or partial remission rates were high, around 70%. It is important to note that the doses used were lower than those used in schizophrenia. To our knowledge there are no dose-response data for any antipsychotic drug in the treatment of delusional disorder. Treatment data on one type of delusional disorder – such as delusional parasitosis – may not be generalized to other types of delusional disorders. Lack of treatment compliance is a major obstacle in the treatment of delusional disorders. Adherence to treatment in schizophrenia seems to be higher with second generation antipsychotics. Long acting intramuscular injection formulations of first generation antipsychotics and the availability of choices and formulations (liquid, dissolvable, acute intramuscular, and long-acting intramuscular) with second generation antipsychotics may offer an opportunity to improve treatment adherence in patients with delusional disorder. The efficacy, safety, and tolerability, as well as the advantages and the limitations of antipsychotic drugs are described in the other chapters of this book on ▸antipsychotic drugs, first generation antipsychotics, and ▸second and third generation antipsychotics.

Pharmacotherapy of delusional disorders needs major development, since the available options have very limited value.

Cross-References

▸First-Generation Antipsychotics
▸Second and Third Generation Antipsychotics

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Depot Antipsychotics

Definition

Some antipsychotics (e.g. clopentixol, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, risperidone) are available as intramascular depot injections. These depot preparations allow for effective plasma levels over periods ranging from 2-4 weeks. Next to providing the convenience for patients not to have to take daily oral medications, injecting depot preparations is also an objective measure of compliance behavior. Given that assuring compliance is one of the key challenges in the long term management of schizophrenia long acting antipsychotics represent an important addition to the pharmacological treatment options of schizophrenia. In such medications the antipsychotic is bound to various carriers from which it is slowly released after being injected into muscle tissue.

Depressive Disorder and Schizophrenia

Definition

Schizophrenic patients frequently suffer from comorbid depressive syndromes. These can either be part of the acute manifestation of the illness or occur during the prodromal period, or as post-psychotic depression. The latter is diagnosed after the symptoms of acute psychosis have subsided and is sometimes interpreted as an adjustment disorder related to the disabilities caused by schizophrenia. Lastly, depression and ▸schizophrenia can occur in parallel in patients suffering from schizoaffective disorder.

Cross-References

▸Postpsychotic Depressive Disorder of Schizophrenia

Dissociative Anesthetics

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Definition

Dissociative anesthesia is a form of anesthesia characterized by ▸catalepsy, ▸catatonia, analgesia, and amnesia. It does not necessarily involve loss of consciousness, and thus does not always imply a state of general anesthesia. Dissociative anesthetics probably produce this state by interfering with the transmission of incoming sensory signals to the cerebral cortex and by interfering with communication between different parts of the central nervous system.

Pharmacological Properties

History

Most dissociative anesthetics are members of the phenyl cyclohexamine group of chemicals. Agents from this group were first used in clinical practice in the 1950s. Early experience with agents from this group, such as ▸phencyclidine and cyclohexamine hydrochloride, showed an unacceptably high incidence of inadequate anesthesia, convulsions, and psychotic symptoms (Pender ▸6). These agents never entered routine clinical practice, but phencyclidine (phenylcyclohexylpiperidine, commonly referred to as PCP or "angel dust") has remained as drug of abuse in many societies. In clinical testing in the 1960s, ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) was shown not to cause convulsions, but was still associated with anesthetic emergence phenomena, such as ▸hallucinations and agitation, albeit of shorter duration. It became commercially available in 1970. There are two optical isomers of ketamine: S(+) ketamine and R(−) ketamine. The S(+)-isomer is approximately three to four times as potent as the R(−)-isomer, probably because of higher affinity of the S(+)-isomer to the phencyclidine binding sites on NMDA receptors (see subsequent text). The S(+) enantiomer may have more pschotomimetic properties (although it is not clear whether this simply reflects its increased potency). Conversely, R (−) ketamine may preferentially bind to opioid receptors (see subsequent text). Although a clinical preparation of the S(+)-isomer is available in some countries, the most common preparation in clinical use is a racemic mixture of the two isomers.

The only other agents with dissociative features still commonly used in clinical practice are nitrous oxide, first used clinically in the 1840s as an inhalational anesthetic, and dextromethorphan, an agent used as an antitussive in cough syrups since 1958. Muscimol (a potent GABAA agonist derived from the amanita muscaria mushroom), and salvinorin A (a κ-opioid receptor agonist derived from the plant salvia divinorum), are also said to be dissociative drugs, and have been used in mystic and religious rituals (Ritual uses of psychoactive drugs).

Mechanisms of Action

The primary direct molecular mechanism of action of ketamine (in common with other dissociative agents such as nitrous oxide, phencyclidine, and dextromethorphan) occur via an antagonist effect at the N-methyl-D-aspartate (NDMA) receptor. It may also act via an agonist effect on κ-opioid receptors (Opioids). (Sharp ▸11) Positron emission tomography (PET) imaging studies suggest that the mechanism of action does not involve binding at the γ-amino butyric acid GABAA receptor. (Salmi et al. ▸9)

Indirect, downstream effects are variable, and somewhat controversial. The subjective effects of ketamine appear to be mediated by increased release of glutamate, (Deakin et al. ▸3) and also by increased dopamine release mediated by a glutamate-dopamine interaction in the posterior cingulate cortex. (Aalto et al. ▸1) Despite its specificity in receptor-ligand interactions noted earlier, ketamine may cause indirect inhibitory effects on GABA-ergic interneurons, resulting in a disinhibiting effect, with a resulting increased release of serotonin, norepinephrine, and dopamine at downstream sites.

The sites at which dissociative agents (such as sub-anesthetic doses of ketamine) produce their neurocognitive and psychotomimetic effects are partly understood. Functional MRI (fMRI) (Magnetic resonance imaging functional studies) in healthy subjects who were given low doses of ketamine have shown that ketamine activates a network of brain regions, including the prefrontal cortex, striatum, and anterior cingulate cortex. Other studies suggest deactivation of the posterior cingulate region. Interestingly, these effects scale with the psychogenic effects of the agent, and are concordant with functional imaging abnormalities observed in patients with ▸schizophrenia (Fletcher et al. ▸4; Pomaral-Clotet et al. ▸7). Despite these data, it remains unclear whether these fMRI findings directly identify the sites of ketamine action, or whether they characterize the downstream effects of the drug. In particular, direct displacement studies with PET, using ^{11}C-labeled *N*-methyl-ketamine as a ligand, do not show clearly concordant patterns with fMRI data. Further, the role of direct vascular effects of the drug remain uncertain, since there are clear discordances in the regional specificity and magnitude of changes in cerebral blood flow, oxygen metabolism, and glucose uptake, as studied by PET in healthy humans. (Langsjo et al. ▸5)

The neurophysiological effects of anesthetic doses of ketamine are different from those of most other anesthetic agents. When used as the sole anesthetic agent, ketamine results in maintained or increased global cerebral metabolism and cerebral blood flow, whereas most anesthetic agents reduce cerebral blood flow and metabolism. The regional cerebrovascular and metabolic effects of anesthetic doses of ketamine have been studied in animal models, and are broadly concordant, but no data are available in

humans. However, the global increases in cerebral blood flow and volume produced by ketamine mean that, in patients with poor intracranial compliance, ketamine can cause increases in intracranial pressure. Electroencephalography shows that electrical activity during ketamine-induced anesthesia is maintained, with alternating periods of high amplitude delta activity and periods of fast activity. Again, when there are regional variations in such effects, their relationship to regional physiology and metabolism, and their neurochemical specificity, are poorly studied in man.

Pharmacokinetics

For medical use, a 10 mg/ml or 50 mg/ml solution is administered by intramuscular injection or, more commonly, by intravenous injection. Being a lipophilic drug, the onset of clinical effects is rapid and the time to peak effect after a bolus intravenous dose is short, suggesting that the drug crosses the blood-brain barrier rapidly. No estimates of the blood-effect-site equilibration rate constant have been published.

The initial volume of distribution is 60–80 L. Ketamine undergoes extensive re-distribution – two and three compartment pharmacokinetic models have been described. Fast re-distribution results in a short duration of action after a bolus dose (half-life 11–17 min). Lipophilicity results in accumulation in the fatty tissues. Published volumes of distribution at steady state are in the range 200–350 L (Reilly ▸8; Sinner and Graf ▸10).

Ketamine undergoes hepatic metabolism. Demethylation results in the major metabolite, norketamine, which possesses sedative and analgesic properties (potency is ~20% of ketamine). After hydroxylation and conjugation, norketamine is excreted by the kidneys. Elimination half-life is 2.5–4 h. Total clearance is ~1,200 mL/min. Despite accumulation, the relatively fast rate of metabolism makes ketamine an ideal agent for use by infusion.

Ketamine in powder form is rapidly absorbed via the mucosal surfaces of the upper airway, and so when used for recreational purposes (Self-administration of drugs) it is usually administered by insufflation. Oral administration is seldom used since mean bioavailability is ~16%, and drug absorbed through the gut mucosa is rapidly metabolized to norketamine, resulting in sedation, which limits the dissociative effects.

Efficacy/Doses

Ketamine is used in clinical practice in two main indications. At moderate doses, it is a powerful analgesic, whereas at higher doses it is used as an anesthetic agent in specific situations (see below). Its ability to block NMDA-receptors has prompted studies investigating its role as a neuroprotective agent, and as a treatment for refractory status epilepticus. Intriguingly, in other settings (particularly in the developing brain and in aged

animals) ketamine has been shown to be neurotoxic. Very low doses of ketamine have found a substantial research role in producing human models of ▸schizophrenia. For analgesia without unconsciousness, intravenous dose requirements are 0.25–0.75 mg/kg, whereas intramuscular dose requirements are ~0.5–2 mg/kg. Bolus doses toward the upper end of the above ranges will result in a dissociated state with sometimes profound psychiatric symptoms (such as the "▸k-hole"). The plasma levels at which psychotomimetic symptoms develop range between 50 and 300 ng/mL, analgesic effects are observed at about 200 ng/mL, whereas anesthesia is achieved at plasma levels above 1,000 ng/mL.

For anesthesia, an intramuscular dose of 8–10 mg/kg will produce loss of consciousness within 5 min, and anesthesia lasting for approximately 30 min. An intravenous dose of 1–2 mg/kg will produce loss of consciousness within 2 min, and anesthesia lasting 10–15 min. After an initial intravenous bolus dose, anesthesia can be maintained with additional bolus doses of 0.5 mg/kg or by an infusion at 1–2 mg/kg/h.

Safety/Tolerability

Ketamine increases in upper airway secretions, which can be attenuated by prior treatment with an anticholinergic agent. It can cause post-operative nausea and vomiting, and is associated with unpleasant dreams and hallucinations on emergence, with nightmares on subsequent days. These psychiatric phenomena can be attenuated by concomitant administration of a benzodiazepine or propofol, an intravenous anesthetic agent that acts at GABA receptors.

When used for recreational purposes, ketamine causes hallucinations, and a dissociative state characterized by depersonalization and derealization. At higher doses, users may experience a constellation of symptoms colloquially known as a "k hole". In clinical studies, infusions of subsedative doses produce several of the negative symptoms of schizophrenia, producing a reversible model for studying its pathogenesis. Such studies have shown that low doses of ketamine can produce impairments in working memory and episodic memory functions found in patients with schizophrenia. (Corlett et al. ▸2)

Compared with other anesthetic agents, respiratory drive, airway reflexes, and ventilation are well maintained with ketamine, although at higher doses respiratory depression and apnoea will eventually occur. Ketamine possesses sympathomimetic properties, resulting in bronchodilation, increases in heart rate, and maintained or increased blood pressure in normovolaemic patients. Very low doses may cause favorable effects on immune functions. Ketamine is a potent analgesic. Subanesthetic doses have been shown to produce postoperative analgesia and to have anti-hyperalgesic activity.

These powerful analgesic properties make it useful in occasional patients with severe chronic pain, unresponsive to first line analgesics. Ketamine may have a role in the prevention of chronic pain when used as an analgesic for acute (typically post-operative) pain, possibly by preventing central sensitization in neural systems. Ketamine has also been used for the treatment of chronic pain, by the oral, parenteral, and spinal routes.

The paucity of cardio-respiratory depressant effects makes ketamine an ideal anesthetic agent for use in poorer countries, where facilities for ventilation and airway management may be limited, and also in trauma situations, where patients may have suffered significant blood loss resulting in hypovolaemia (and in whom other anesthetic agents may result in significant falls in blood pressure). In children, it is sometimes used by intramuscular injection for sedation where intravenous access is difficult to achieve. The analgesic properties can make ketamine a useful agent for short-term sedation or dissociative anesthesia for painful procedures, such as burns dressing changes.

Conclusion

Recreational use of ketamine is common in many countries. In contrast, the use of dissociative anesthesia is becoming increasingly rare in the first world, since adequate sedation, analgesia, and anesthesia can be achieved with one or more newer agents with fewer adverse effects. However, ketamine is being used increasingly as an adjuvant analgesic during general anesthesia. The adverse psychiatric effects that limit its use in clinical practice do, however, provide a useful model for investigating the cognitive deficits and pathogenesis of schizophrenia. Functional imaging studies can identify the neuroanatomical sites at which altered cognitive function occurs in subjects receiving ketamine, and may thus identify the areas where altered function results in the behavioral and cognitive changes common to schizophrenia and low-dose ketamine administration. Finally, in chronic pain studies, ketamine may provide insights into the pathogenesis of chronic pain, and may have a role in the prevention and treatment of chronic pain.

Cross-References

▸K-Hole
▸Schizophrenia

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Dopamine

Synonyms

DA

Definition

A major modulatory brain monoamine neurotransmitter released by axons of cell groups located in the midbrain and other deep brain areas, and synthesized in the brain from the amino acid tyrosine. It is an intermediate step in the synthesis of norepinephrine and epinephrine. Four dopaminergic pathways have been localized in the central nervous system: mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular. Furthermore, five receptors have identified (D1–D5) within two families: D1 (D1, D5), D2 (D2,

D3, D4). Extracellular dopamine levels are regulated by at least two mechanisms: the dopamine transporter, which recycles dopamine into the presynaptic terminal, and the enzyme catechol-*O*-methyltransferase, which degrades extracellular dopamine and norepinephrine.
Dopaminergic projections reach many regions of the brain, especially the dorsal striatum, where dopamine participates in the selection of motor actions; the ventral striatum or nucleus accumbens, involved in motivation and prediction of future rewards; the amygdala, processing emotional reactions, and the cerebral cortex (especially prefrontal), where dopamine regulates executive functions like attention and working memory. Thus, via its interactions with glutamate and GABA-based synaptic transmission in these regions, dopamine plays a key role in attention, cognition, motivation, and both pharmacological and biological rewards, as well as in sensory and motor functions. Dopamine is implicated in Parkinson's disease, ▸schizophrenia, and drug dependence. It has long been hypothesized that at least the positive symptoms of schizophrenia (e.g., delusions, hallucinations) reflect hyperdopaminergic activity. The dopamine D2 receptor has been tied to this effect and all available antipsychotics demonstrate some degree of dopamine D2 blockade. The D3 receptor has also been implicated in psychosis, while the D1 receptor is involved in cognitive processes. The majority of abused drugs target dopaminergic synapses in the ventral striatum, inducing an increase of dopaminergic signaling.

Dopamine Hypothesis

Definition

The dopamine hypothesis of schizophrenia and other psychoses – including delusional disorders – states that these disorders are related to a dysfunction of the dopamine system in the brain. Positive symptoms, such as delusions and hallucinations are linked to dopamine "hyperfunction" (to hyperactive signal transduction).

Dysbindin

Synonyms

Dystrobrevin-binding protein 1

Definition

Dysbindin is a protein constituent of the dystrophin-associated protein complex of skeletal muscle cells. Dysbindin is found in neural tissue of the brain, especially in axon bundles and particularly in certain axon terminals, notably mossy fiber synaptic terminals in the cerebellum and hippocampus. Pedigree-based family-association studies of families with a history of schizophrenia have shown a strong association between expression of a particular dysbindin allele and a clinical expression of schizophrenia. However, the exact link between dysbindin and schizophrenia remains highly controversial.

Cross-References

▸Antipsychotic Medication: Future Prospects
▸Schizophrenia

Early Ventral Hippocampal Lesion Model

Definition

An animal model in which the ventral hippocampal region in rats is lesioned using an excitotoxic agent. This lesion is performed at an early age (typically postnatal day 7). These animals develop several schizophrenia-like phenomena in adulthood. Interestingly, most of the symptoms occur after puberty in accordance with the clinical literature on schizophrenia.

EUFEST

Synonyms

European first episode in schizophrenia trial

Definition

An open, randomized clinical trial of a low-dose of haloperidol (1–4 mg) versus SGA in first-episode schizophrenia. This pragmatic trial found lower discontinuation rate with SGA than with haloperidol. However, symptom reductions were virtually the same in all the groups, at around 60%.

Cross-References

- ▸Antipsychotic Drugs
- ▸First-Generation Antipsychotics
- ▸Second- and third-generation antipsychotics
- ▸Haloperidol
- ▸Schizophrenia

Extrapyramidal Motor Side Effects

Synonyms

EPS

Definition

The extrapyramidal system is a neural network located in the central nervous system, which is involved in the coordination of movement. Extrapyramidal symptoms refers most commonly to the side effects of many antipsychotics that affect movements. They include neurologic syndromes such as dystonia, dyskinesia, Parkinson-like disturbances including tremor, rigidity, and bradykinesia as well as akathisia. These adverse events can oc-

cur both during acute and the chronic treatment with antipsychotics. They are sequelae of the dopamine antagonist properties of antipsychotics. In general, they are dose-dependent and more severe and frequent with first-generation antipsychotics than with the newer drugs.

Cross-References

▸Antipsychotic Drugs
▸First-Generation Antipsychotics
▸Second- and third-generation antipsychotics
▸Tardive Dyskinesia

Family Based Approaches for Schizophrenia Patients

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Synonyms

Family psychoeducational interventions for schizophrenia; Family supportive interventions for schizophrenia; Family cognitive-behavioural interventions for schizophrenia.

Definition

Family intervention is a psychological therapy to help families to cope with schizophrenia and other severe mental disorders, using a cognitive-behavioural model. It improves outcomes by reducing relapses and hospitalizations.

Introduction

The shift of mental health provision from hospital-based to the community for patients with severe mental disorders has resulted in the recognition and acceptance of the major role played by families in the recovery process of their mentally ill relatives. About 60 of seriously mentally ill persons live with their families, with high levels of stress associated with the practical and psychological burden imposed on all family members.

In the past 30 years, research on Expressed Emotions (EE), the adoption of the stress-vulnerability model of schizophrenia, the development of the family burden construct and the acknowledgement that the family atmosphere has a significant role in relapses in schizophrenia have led to the development of a number of family interventions (Falloon, ▸5). Different models of family interventions have been developed to meet the different needs of families, and they mainly include psychoeducation, family education and family consultation. All these approaches differ from traditional family therapy in that they do not treat families as part of the problem; instead, they see them as part of the solution. In this chapter we will focus on family psychoeducation, which represents the intervention with the greatest empirical support from randomized controlled trials and meta-analyses. Definitions of the other two approaches will be provided at the end of the chapter.

Family psychoeducational interventions

There are many family psychoeducational interventions developed for the treatment of patients with schizophrenia and their relatives. The most com-

monly used approaches are those developed by Falloon, Hogarty, McFarlane, and Tarrier & Barrowclough (Pharoah et al, ▸10). All the different models of family psychoeducational interventions are based on the cognitive-behavioural individual therapy and on individual psychoeducation. They share the goal of reducing relapses and improving the quality of life for both the patients and their family members. They also share the following basic aims: a) to provide the family with information about the diagnosis, symptoms, signs, etiology, course and treatment, including medications and the management of their side effects; b) to improve communication patterns within the family; c) to enhance the problem solving and coping strategies of families; d) to encourage all family members to be involved in social and leisure activities (Solomon and Cullen, ▸12).

However, these approaches may differ in several aspects of program implementation, including: a) the use of single vs. multiple-family approaches; b) the location of service provision (i.e., family's home, clinic, outpatient unit, hospital); c) the length of the intervention (which varies from 12 to 48 sessions, provided weekly to monthly, over 6 to 24 months); d) credentials and qualifications of providers; e) the content emphasized and the information provided; f) the focus on problem-solving, communication skills or behavioural management; g) the relatives involved; h) the delivery of information; i) the involvement of the ill relative in the intervention (Fadden, ▸4). Despite this huge variation among the different models, common elements in content have been identified, and they are reported in Table 1.

Research on the different family psychoeducational models has not resulted in determining which one is superior to others. This is probably due to the fact that since these models have so much in common such a distinction is not possible (Solomon & Cullen, ▸12). However, the Falloon model is the most frequently adopted approach when the intervention is provided in an individual format, while the McFarlane approach represents the most frequently used group model.

Table 1 Content of psychoeducational family interventions (adapted from Fadden, ▸4, and from Solomon and Cullen, ▸12)

A collaborative relationship between family and therapists
Highly structured interventions
Information-sharing and agreement about confidentiality
Education about the illness, its course and treatment
Time and space for discussion of emotional issues and personal reactions to the mental health problems and their management
Support for family members in the achievement of personal goals

(Continued)

Focus on the management of practical day-to-day issues
Teaching coping skills and strategies
Enhancement of family problem-solving skills
Teaching of relapse prevention strategies
Teaching families communication techniques
Use of a behavioral approach

Efficacy of family psychoeducational interventions

A number of published studies have demonstrated the clinical efficacy of family psychoeducational interventions for persons with schizophrenia, in particular in preventing psychotic relapses and hospitalizations. Patients whose families receive this intervention have a relapse rate at one year ranging from 6 to 12, compared with 41 to 53 of relapses in those not receiving it. At two years the results are less evident, suggesting that this intervention may delay rather than prevent relapses (Dixon et al, ▸1; McFarlane et al, ▸8), or that they loose efficacy over time by an extinction effect, requiring more long-term studies. In addition, family psychoeducational interventions were found to be effective in improving patients' compliance to drug treatments and in reducing the overall costs of care, patients' disability and family burden (Dixon et al, ▸2).

Results of randomized controlled trials have been confirmed by several reviews and meta-analyses reporting that these interventions, compared to routine case management, yield a fourfold reduction of patients' relapse rate at one year and a twofold reduction at two years (NICE, ▸9; Royal Australian and New Zealand College of Psychiatrists, ▸11; Pharoah et al, ▸10; Dixon et al, ▸3).

According to the NICE guidelines on the treatment of schizophrenia (▸9), "family interventions to be offered to 100 of families of individuals with schizophrenia who have experienced a recent relapse, are considered to be at risk of relapsing, or who have persisting symptoms, and are living with or are in close contact with their family. All individuals who receive family interventions should be offered more than 10 sessions, the course of treatment lasting for more than six months".

However, in spite of the evidence supporting these approaches, they are not routinely available in clinical practice (Falloon, ▸6). In Western Europe, the number of families of patients with schizophrenia receiving them in routine settings ranges between 0 and 15; in USA, this percentage is about 10; in Italy – the country with the longest experience in community mental health care – although 80 of the families of patients with schizophrenia have regular contacts with the local mental health centre, only 8 of them receive these interventions. Therefore, there is limited evidence as to the effectiveness of

these interventions in practice. In the last decade effectiveness studies have been carried out to identify the best strategies to implement this evidence-based intervention in routine settings, and they are reported in the following section.

Implementation of family psychoeducational interventions in routine settings

Despite the evidence of the efficacy of family psychoeducational interventions, many mental health services struggle to ensure that the needs of families are met. One of the big issues is related to the training and confidence of staff in adult mental health and rehabilitation services offering support to families. Training in the skills needed to work with families of severely mentally patients is inadequate in all professional training courses. Studies of staff members who attended training courses indicate that about a third of those trained do not implement work with families following training. There is now a clear recognition that the effective implementation of family work requires a completely different approach, in which the issue is rather addressed at an organizational level, with close involvement of managers.

Recently, several studies have been carried out, both at national and international levels, to investigate the best strategies to ensure that patients and their relatives receive family psychoeducational interventions.

In the years 2000-2004, the European Commission promoted a study to assess the impact of a standard and an augmented staff training programmes on the implementation and effectiveness of psychoeducational family intervention for schizophrenia. This study, carried out in six European countries – Italy, UK, Germany, Greece, Portugal, and Spain – aimed to explore the possibility of providing psychoeducational intervention for schizophrenia in routine settings, as well as difficulties and benefits experienced by professionals in the implementation process (Magliano et al, ▸7). Both programmes included a basic course on single-family psychoeducational intervention, and nine supervision sessions in the subsequent year. The augmented programme also included training sessions on the use of communication and problem solving skills by the staff to cope with implementation problems and homework on psychoeducational techniques. The standard training programme consisted of a five-day full time workshop, while the augmented one consisted in three monthly modules of two days each. In the six participating countries, a national leading centre had to randomly select four mental health centres, which were randomly allocated to attend one of the two training courses and to implement the intervention in their centres for one year.

F

A total of 48 professionals were trained in the use of psychoeducational family intervention. They reported a significant improvement in their relationships with patients and families, and in clinical results. The most frequent difficulties reported by the professionals were work overload, difficulty in integrating family work with other responsibilities, and poor allowance of time to run the intervention. No significant differences in trainees' advantages and difficulties related to the attendance of one of the training programmes were observed. The conclusion of this multisite study is that without a clear focus on organizational issues, it is unlikely that the culture will change or that those trained will be able to put their newly acquired skills into practice.

Other family supportive interventions

Given the difficulties in implementing structured family psychoeducational interventions, in order to provide support to relatives of persons with schizophrenia, other approaches have been recently developed, namely family education and family consultation.

Family education is a non-clinical intervention whose primary aim is to meet the educational and practical needs of the family. It is a group intervention that is open to anyone with a relative or a significant other who has a severe mental illness. This program is usually community-oriented and often led by family members, although professionals are frequently involved in the discussion of specific topics, such as medications (Solomon and Cullen, ▸12). Family education programs take into account the phase of the patient's illness, the life cycle of both the patient and the family, and the family's cultural context. It is a very brief intervention derived from the psychoeducational approach, and its efficacy has not yet been documented by clinical trials.

Family consultation in an individual approach aimed at providing information, advice, support and counseling to either an individual family member or to the family as a whole. The ill relative is usually not present in these meetings. The provider is usually a mental health professional, but may also be a trained family member. The consultation may be provided over the telephone, but it is usually provided in person. Families report that having a consultant available is extremely helpful. However, efficacy studies on this intervention are lacking.

Conclusions

The favorable effects of psychoeducational family interventions on patients' clinical status and disability are now well documented, although it seems that they tend to disappear over time. It is likely that the inclusion of booster sessions at the end of the intervention protocol may favour the maintenance

of relatives' communication and problem solving acquired skills, reducing the probable extinction effect. These recall sessions could be provided in a multi-family format, with a lower investment of resources by the services and with an indirect reinforcement of the family social network. Although the different models of psychoeducational family interventions show significant effects on patients' conditions, the single-family approach seems to be associated with a higher adherence to treatments, which is a crucial issue in the management of patients with schizophrenia. On the other hand, the multi-family approach has shown to be more cost-effective, and therefore a combination of the models may be needed. However, this clearly requires further investigations.

No study has specifically compared the effects of psychoeducational family interventions provided for different lengths of time (e.g., 9 months vs. two years) or intensity (e.g., biweekly vs. monthly sessions). Therefore, what is the "best exposure dose" of this intervention still needs to be clarified, even if the NICE guidelines suggest that 10 sessions in six months are the minimum effective "dose".

Further studies are needed to address these issues in order to facilitate the dissemination on a large-scale of psychoeducational family interventions for schizophrenia.

The effects of family education and family consultation still need to be investigated. However, they appear as promising interventions, in particular given their feasibility and the low use of needed resources.

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First-Generation Antipsychotics

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Synonyms

Classical antipsychotics
Classical neuroleptics
Conventional antipsychotics
Conventional neuroleptics
Major tranquilizers
Old antipsychotics
Old neuroleptics

Traditional antipsychotics
Traditional neuroleptics
▸Typical antipsychotics
Typical neuroleptics

Definition

Antipsychotics introduced to the market in USA before ▸Clozapine (before, 1989).

Pharmacological Properties

▸First-generation antipsychotics (FGA) is a heterogeneous group of ▸dopamine D2 receptor antagonists with different chemical, pharmacological and clinical profile. Main clinical characteristic of the FGA is more Extrapyramidal Motor Side-Effects (EPSE), more frequent hyperprolactinaemia and less clinical efficacy if compared with the ▸second-generation antipsychotics (SGA). There are, however, some exceptions from and inconsistencies in the definition above. For example ▸amisulpride and ▸risperidone, two SGA significantly increase prolactin levels and so some authors do not acknowledge hyperprolactinaemia as a good group differentiating factor. Moreover, clinical comparison of FGA and SGA gives ambiguous results. Today it is clearer that there are not sharp boundaries between FGA and SGA and maybe in the near feature more pertinent classification will be adopted.

Chemical Profile

Using chemical profiles FGA can be classified as ▸butyrophenones (e.g., ▸haloperidol, ▸bromperidol, ▸benperidol, droperidol, pipamperone, spiperone, trifluperidol).
Dibenzoxazepines: loxapine. Diphenylbuthylpiperidines: fluspirilene, penfluridol, ▸pimozide. ▸Phenothiazines (e.g., ▸chlorpromazine, clopenthixole, fluphenazine, metophenazate, metotrimeprazine, periciazine, ▸perphenazine, ▸prochlorperazine, promazine, promethazine, prothipendyle, ▸thioridazine, ▸trifluoperazine, triflupromazine. Substituted benzamides: ▸sulpiride. *Other tricyclic antipsychotics*: ▸carpipramine, clorotepine, oxyprothepine. ▸Thioxanthenes (e.g., chlorprothixene, cisclopenthixole, flupenthixole, ▸thiothixene, zuclopenthixole).
Many of these compounds are no more on the market.

Low and High Potency Antipsychotics

From clinical as well as pharmacological point of view FGA can be classified as *high-potency* and *low-potency* antipsychotics. Potency refers to their affinity to dopamine D2 receptors and the average therapeutic dose, com-

pared with a 100 mg of chlorpromazine (so called chlorpromazine equivalent) (Baldessarini et al. ▸1). The example of low-potency antipsychotics in light of evidence based medicine is chlorpromazine (Leucht et al. ▸5). Low potency antipsychotics have been suggested to be more sedative than high potency antipsychotics but on the other hand induce less EPSE than high-potency antipsychotics. In sufficiently high doses, low potency antipsychotics are not, in principle, less effective than high potency antipsychotics such as haloperidol (Leucht et al. ▸5). Low-potency antipsychotics induce more EPSE than ▸clozapine, ▸olanzapine and risperidone but not more than other SGA (Leucht et al. ▸6). Low-potency antipsychotic are less sedative than ▸clozapine, NNH (Number Need to Harm) 13 [7–220], but do not differ in this respect from other SGA (Leucht et al. ▸6). Weight gain is similar to that after SGA and higher than after ▸aripiprazole and ▸ziprasidone (Leucht et al. ▸6).

High-potency antipsychotics induce more EPSE than low-potency antipsychotics and SGA. The typical representative of this group is haloperidol. NNH for haloperidol to induce EPSE was between 2 for clozapine and 5 for zotepine (Leucht et al. ▸6). On the other hand haloperidol was associated with less weight gain than most of SGA and was not different from aripiprazole and ziprasidone in this respect (Leucht et al. ▸6). Haloperidol was significantly less sedating than clozapine (NNH 5 [3–14]), ▸quetiapine (NNH 13 [8–20]), and zotepine (NNH not significant) but significantly more sedating than aripiprazole (NNH 33 [20–1,001]; (Leucht et al. ▸6)).

Efficacy of the FGA

The recent meta-analyzes concluded that the FGA as a group were less efficacious than some but not all antipsychotics from SGA (Leucht et al. ▸6). In Leucht et al. (▸6) meta-analysis 95 studies were included with haloperidol, 28 studies with chlorpromazine, five studies with perphenazine and less than five with other FGA. So results from this meta-analysis are more related to haloperidol or chlorpromazine than to other FGA. In the concrete, FGA was less effective in overall change of symptoms than ▸amisulpride, ▸clozapine, ▸olanzapine, and ▸risperidone; in the management of positive symptoms FGA were less effective than amisulpride, clozapine, olanzapine, quetiapine, and risperidone; in the management of negative symptoms FGA were less effective than amisulpride, clozapine, olanzapine and risperidone, and in alleviation of depression FGA were less effective than amisulpride, aripiprazole, clozapine, olanzapine and quetiapine (Leucht et al. ▸6). FGA are less effective in long term treatment of schizophrenia than olanzapine (NNT 17 [8–100]), risperidone (NNT 11 [7–33]), and sertindole (NNT 14 [8–50]). FGA improve quality of life less than amisulpride, clozapine and sertindole (Leucht et al. ▸6).

Naturalistic (Effectiveness) Studies

Results from real world effectiveness studies such as ▸CATIE (Rosenheck et al. ▸8), and ▸CUtLASS (Jones et al. ▸2) suggest that mid-potency FGA compounds would have been more appropriate, because they are less likely to cause EPSE and they are not associated with sedation and weight gain. The representatives of this group are ▸perphenazine and ▸sulpiride. Efficacy of SGA was not better than perphenazine on PANNS total score (Rosenheck et al. ▸8), cognition (Keefe et al. ▸4), cost (Rosenheck et al. ▸8), quality of life, and psychosocial functioning (Swartz et al. ▸9).

Another pragmatic trial (EUFEST) compared the effectiveness of SGA with that of a low dose of haloperidol (1–4 mg), in the first-episode schizophrenia (Kahn et al. ▸3). This pragmatic trial found lower discontinuation rate with SGA than with haloperidol. However, symptom reductions were virtually the same (about 60%) in all groups. Despite the fact that the difference in discontinuation rates was the primary outcome variable one cannot definitively conclude that SGA are more efficacious than is the low dose haloperidol in first-episode schizophrenia, since discontinuation rates are not necessarily consistent with symptomatic improvement.

Other Side Effects of the FGA

There are other typical side effects of the FGA than only EPSE and hyperprolactinaemia. These side effects are observed mainly in low-potency antipsychotics and are related to anticholinergic, antiadrenergic and antihistaminic activity. Anticholinergic activity of low-potency antipsychotics leads to dry mouth, blurred vision, difficulty passing urine, urinary retention, constipation, glaucoma and rarely ileus. Antiadrenergic activity can induce postural hypotension, reflex tachycardia, and sexual dysfunction (particularly erectile dysfunction). Antihistaminic activity is responsible for sedative effect and weight gain. Idiosyncratic side effects are: leucopenia or agranulocytosis, cholestatic jaundice, altered glucose tolerance, skin photosensitivity (sun block is important in sunny weather), pigmentation to skin or to eye, neuroleptic malignant syndrome. Some FGA can lower seizure threshold (i.e., chlorpromazine) or could prolong QT interval (chlorpromazine, droperidol, pimozide, thioridazine).

Cross-References

▸Amisulpride
▸Antipsychotic Drugs
▸Aripiprazole
▸Benperidol
▸Bromperidol
▸Butyrophenones

▸Carpipramine
▸CATIE
▸Chlorpromazine
▸Clozapine
▸CUtLASS
▸EUFEST
▸Floropipamide
▸Haloperidol
▸Olanzapine
▸Pericyazine
▸Perphenazine
▸Phenothiazines
▸Pimozide
▸Prochlorperazine
▸Quetiapine
▸Risperidone
▸Second-Generation Antipsychotics
▸Sulpiride
▸Thioridazine
▸Thiothixene
▸Thioxanthenes
▸Trifluoperazine
▸Ziprasidone

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First-Rank Schizophrenic Symptoms

Definition

Psychopathological symptoms like delusional perceptions, commenting auditory hallucinations, thought withdrawal, thought broadcasting, etc., which are strongly associated with schizophrenia, if a somatic cause is not present.

Floropipamide

Definition

Floropipamide is a first-generation (typical) antipsychotic drug that belongs to the butyrophenone type indicated for the treatment of schizophrenia.

However, it possesses more potent antagonist properties at 5-HT2A than D2 receptors. It can induce extrapyramidal motor side effects, hypotension, and fatigue, but it displays generally low toxicity. Extrapyramidal side effects with floropipamide appear to be less common than with other butyrophenones.

Cross-References

▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics
▸Schizophrenia

Flupenthixol

Definition

Flupenthixol is a typical thioxanthene antipsychotic, sharing similar profile to phenothiazines. It acts as an antagonist at D1 and D2 dopamine receptors, as well as α-adrenergic receptors. Its antipsychotic effects are thought to result from postsynaptic D2 receptor blockade. Due to its long-acting nature (elimination half-life ranging from 5 to 113 days after depot injection), flupenthixol is often used for maintenance treatment of schizophrenia. As with other typical antipsychotics, flupenthixol is associated with a high incidence of extrapyramidal symptoms, but it has less anticholinergic effects. Like many other antipsychotic agonists, it has also been used in experimental psychopharmacology to test the importance of dopamine receptors in various physiological and psychological phenomena; the different selectivity of the (+)- and (−)-isomers has to be taken into account.

Cross-References

▸First-Generation Antipsychotics

Functional Outcome

Definition

Functional outcome distinguishes itself from clinical outcome, focused instead of an individual's recovery in areas such as vocational and social functioning rather than symptom resolution. Its measurement speaks to the impact of severe and chronic illnesses, such as ▸schizophrenia, and a growing awareness that functional and clinical recovery do not necessarily parallel each other.

With schizophrenia, it was held for many years that the positive symptoms (e.g., delusions, hallucinations) were central to the gradual decline in functioning commonly seen over the course of the illness. However, more recent evidence suggests that other features of this illness, for example, deficit (negative) symptoms and neurocognitive changes, may play a more critical role in compromising functional recovery. This has diminished focus on positive symptoms and the implicit assumption that their resolution ensures a return to premorbid level of functioning and, in so doing, has forced a reconceptualization of schizophrenia and expanded current treatment/research strategies.

Cross-References

▸Cognitive Behavioral Therapy for People with Schizophrenia
▸Cognitive Remediation
▸Rehabilitation in Schizophrenia
▸Schizophrenia

Hallucinations

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Definition

Hallucinations are perceptions without objective reality; that is, in the waking state, sensory events are experienced, which are unfounded but appear to emanate from external space. Hallucinations can develop in any sensory modality but most commonly are visual or auditory in nature. They can be simple, for example patterns or noises, or complex, for example images of people, objects and scenes, voices of people speaking in coherent sentences, or musical recitals.

Hallucinations normally develop in association with other mental state abnormalities, when there is a medical condition adversely affecting brain function. However, they can also occur as isolated phenomena in people who are otherwise normal. For example, it is not uncommon to experience the physical presence or voice of a deceased loved one in the early stages of bereavement. Auditory or visual hallucinations can also be experienced when waking-up or falling asleep and are known as hypnopompic and hypnagogic hallucinations, respectively. Even a small percentage of the general public report hearing voices on a fairly regular basis when going about their daily routine. In these circumstances, hallucinatory experiences are usually transient or mild and do not give rise to significant distress. When people who experience hallucinations come to medical attention, it is usually because they are vivid, frequent and intrusive, and when insight into their veracity is lost.

Hallucinations can arise during the course of an organic disorder, usually in the context of diffuse cerebral cortical dysfunction, as in states of delirium where consciousness is impaired due to a metabolic derangement or a toxic influence. Notable examples are the alcohol withdrawal states of delirium tremens, when vivid visual hallucinations of animals are commonly experienced ("pink elephants") as well as tactile hallucinations of insects burrowing into the skin (formication), and alcoholic hallucinosis, when intense persecutory voices are heard. Hallucinations also commonly develop in organic disorders where consciousness is not impaired but when there is a widespread neurodegeneration of the cerebral cortex, as in Lewy body de-

mentia or Alzheimer's disease. However, it is the study of hallucinations occurring in more rare circumstances, when there is specific focal pathology, which has provided important information concerning their neural basis. This has shown that hallucinations can arise when there is an abnormality in the sensory pathway corresponding to the modality of the hallucination itself which can be located anywhere from the primary sensory organ to the secondary sensory association cortex. Hence, the Charles Bonnet syndrome, in which vivid visual hallucinations of people, animals, or scenery are experienced, is most often associated with acquired damage to the retina or optic nerve. An auditory equivalent, musical hallucinosis, has been described in acquired deafness. Subcortical lesions of the thalamus, cerebral peduncles, and brainstem, due to tumor or infarction, can also give rise to complex visual or auditory hallucinations, presumably due to the transection of modality-specific ascending sensory nerve fibers (Braun et al. ▸2). A common finding in functional neuroimaging studies of these disorders is that, even when the pathological locus is "downstream", there is increased activity in the corresponding modality-specific secondary association cortex (Allen et al. ▸1). Secondary sensory association cortex is the area in which sensory stimuli are organized into coherent percepts, having been processed in fragmented form in primary sensory cortex. Thus, one explanation is that secondary association cortex spontaneously generates images or false perceptions using "top down" input from memory circuitry in an attempt to make sense of reduced or aberrant sensory input (Allen et al. ▸1; Braun et al. ▸2; Frith and Dolan ▸4).

In the lesion cases described above, insight into the hallucinatory nature of experiences is often retained. When insight is disturbed and hallucinations are regarded as real, a disturbance of supra-modal association cortex is implicated, especially that of the frontal lobe. This has largely been demonstrated by the study of hallucinations in mental illnesses (Allen et al. ▸1) known as "functional psychoses" because there is no obvious associated organic pathology. Schizophrenia is the most prominent example of such a disorder in which hallucinations of voices discussing the person in a derogatory fashion or commenting on their actions are core symptoms. One view is that neural processing in circuitry, critically involving dorsolateral prefrontal and anterior cingulate cortexes, is weakened as part of the neurobiology of the disorder. This circuitry is considered to be involved in monitoring and assigning significance to information being processed elsewhere and instigating actions accordingly. Central to this function is distinguishing whether events or actions, e.g., images or thoughts, are generated by the self or not. This is consistent with an influential psychological explanation of hallucinations by Frith (▸3) as being the product of a

failure of self-monitoring. That is, the failure to recognize that actions such as inner speech are initiated by the self results in them being misattributed to external agencies.

Delusions are false beliefs that are held with complete conviction, unaffected by clear evidence to the contrary and implausible or bizarre. For a belief to be considered a delusion, it should additionally not be shared by other members of the culture from which the individual who holds it originates. Delusions commonly occur alongside hallucinations as part of the spectrum of psychotic phenomena. Like hallucinations, they can arise in the context of organic disorders affecting cerebral function or mental illness. Again, like hallucinations, there are different forms of delusions typified by their content and sometimes associated with specific disorders.

The most frequent type of delusion is self-referential in nature. Paranoid delusions are the most common, witnessed in many organic or functional psychoses, and characteristically are imbued with fear and anxiety. Thus, persecutory delusions include beliefs about being threatened, deceived, or conspired against, and delusions of reference are beliefs that every day events, such as those reported on the TV or in newspapers, are about them. Delusions associated with an abnormally elevated or depressed mood are seen in the affective psychoses. Hence, grandiose delusions are typical of the manic state in bipolar disorder and concern an inflated sense of self-importance such as having special powers or being chosen by God for a special purpose. In psychotic depression, delusions of guilt, that one has committed a heinous crime or is responsible for some disaster; hypochondriasis, that body parts are failing or rotting; and nihilistic delusions, that the self or other people do not exist, are characteristic.

Another set of delusions known as "first rank symptoms" (Sims ▸8) are more characteristic of ▸schizophrenia. These cannot be understood to arise from ordinary life experience and, so long as there is accompanying social or occupational dysfunction, are alone sufficient for the diagnosis. These concern the belief that thoughts, feelings, or actions are under the control of outside forces. For example, thoughts may be inserted, withdrawn, or broadcast to the outside world and actions may be "made" or externally directed (also known as somatic passivity).

Current Concepts and State of Knowledge

The Neurochemistry of Hallucinations and Delusions

Insight into the neurochemical basis of hallucinations comes from the study of Parkinson's disease (PD) in which the primary pathology is degeneration of the ascending midbrain ▸dopamine projections to basal ganglia and cortex. Hallucinations develop in up to 40% of patients and are mainly visual.

In most cases, these are directly attributable to the dose of antiparkinsonian medication as they recede when this is reduced. Studies have shown that the direct dopamine D2 receptor agonists are most likely to induce hallucinations in susceptible individuals but hallucinations have also been reported with other antiparkinsonian drugs, including 3,4-dihydroxy-l-phenylalanine l-DOPA, anticholinergic compounds, amantadine, monoamine oxidase-B inhibitors, and catechol-methyltransferase inhibitors, all of which have the common action of enhancing dopamine neurotransmission. One explanation is that in some cases, doses that are effective in treating the PD movement disorder, which is due to nigrostriatal dopamine depletion, may cause overstimulation of the mesolimbic/mesocortical dopamine system and that this mediates the emergence of hallucinations.

Other evidence supports a central role of abnormal dopamine neurotransmission not only in the development of hallucinations but also delusions. Indirect dopamine agonists, such as amphetamine and methylphenidate, administered at doses that are ineffective in healthy subjects, have been found to worsen both of these psychotic phenomena in schizophrenia (Lieberman et al. ▸7). In addition, it has been known for several decades that drugs that block dopamine D2 receptors, for example the typical or ▸first-generation antipsychotics, such as ▸haloperidol, are efficacious in the treatment of hallucinations and delusions, regardless of the context in which they occur. The atypical or ▸second-generation antipsychotics are also efficacious in this respect. Although these have heterogeneous pharmacological profiles including the blockade of serotonin receptors or other dopamine receptors, they share the common mechanism of D2 receptor blockade.

Other neurotransmitters have also been implicated as mediators of psychotic symptoms but less strongly than dopamine. This is based on self-reports of individuals under the influence of psychoactive drugs. Specifically, the so-called ▸hallucinogens, lysergic acid diethylamide (LSD), psilocybin, and mescaline, are all 5-hydroxytryptamine 2A (5-HT2A) receptor agonists suggesting a role for serotonin; the anesthetic drugs ketamine and ▸phencyclidine are both N-methyl d-aspartate (NMDA) antagonists suggesting glutamate neurotransmission also plays a part. These compounds most often produce dissociated states and altered perceptions in the form of visual illusions or simple hallucinations rather than the more complex hallucinations and delusions experienced in organic and mental illness. Nevertheless, the known interactions between ▸dopamine, serotonin, and glutamate in the modulation of neural processing in circuitry involving frontal cortex, thought to be abnormal in patients experiencing

psychotic symptoms, substantiates the involvement of neurotransmitters other than dopamine in psychosis.

The Dopamine Hypothesis of Psychosis

Two variants of the dopamine hypothesis have been proposed: the postsynaptic variant proposes that abnormal dopamine transmission is related to hypersensitive D2 receptors; the presynaptic variant holds that abnormal dopamine transmission is related to elevated dopamine synthesis or release. While initial molecular imaging studies using [^{123}I]IBZM-SPECT (single-photon emission computed tomography, SPECT) were suggestive of abnormally elevated D2 receptor binding in schizophrenia, later studies that included unmedicated patients produced negative findings, suggesting that antipsychotic medication may have been an important confound in early work. However, several positron emission tomography (PET) studies, for example using [^{18}F]-DOPA, have provided evidence for elevations in presynaptic dopamine availability, even in antipsychotic-naïve patients and patients in the prodrome for psychosis (Howes et al. ▸5). Furthermore, studies that measured stimulant-induced dopamine release in antipsychotic-naïve patients with schizophrenia have reported not only that dopamine release is elevated in these patients, but that the extent of dopamine release is strongly related to the increase in psychotic symptoms following stimulant administration. Together, these findings reinforce the importance of dopamine in the generation of psychotic symptoms, particularly delusions. However, there remains a gap in understanding the mechanism by which increased dopamine release might cause an individual to develop such persistent and irrational false beliefs.

In order to fill this gap, a number of theorists have sought to explain the link between dopamine and delusions by appealing to the function of dopamine in the healthy brain. Many studies have suggested that while dopamine is not necessarily released when rewards (e.g., food) are actually delivered, it is released when rewards are expected. Others have suggested that dopamine may act as a teaching signal during reward learning. In particular, it has been suggested that dopamine release mediates motivational salience in the brain, i.e., the ability of stimuli associated with reward to drive goal-directed behavior. Salient stimuli are those that stand out from their surroundings and automatically capture attention due to some distinguishing characteristics, be it perceptual contrast, novelty, surprise, or emotional association. Recent evidence suggests that novelty salience may also trigger dopamine neuron firing, raising the possibility that dopamine may play a more general role in encoding salience in the brain.

Appealing to this notion of dopamine as a general signal for salience, a recent hypothesis suggested that psychosis and, in particular, delusions might be

related to a state of "aberrant salience", driven by poorly regulated dopamine release (Kapur ▸6). In this framework, the release of dopamine out-of-context with the environmental surroundings leads to the tagging of irrelevant stimuli as salient, leading individuals to attribute to them some importance or relevance. In this framework, a delusion is conceptualized as the post-hoc rationalization of accumulated aberrant salience experiences. One of the strengths of this hypothesis is that it explains why delusions take some time to resolve following the onset of antipsychotic medication. It suggests that antipsychotics do not treat delusions directly, but instead limit the aberrant salience experiences that cultivate them, allowing delusions to extinguish gradually. It also explains why patients dislike taking antipsychotic medication, since both aberrant and normal motivational salience processes will be affected by D2 blockade, resulting in a state in which individuals experience a lack of motivation or energy. However, further work is required to test the numerous predictions made by this influential hypothesis.

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▸Schizophrenia

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Hallucinogen Abuse and Dependence

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Definition

Hallucinogen abuse and dependence are known complications resulting from the illicit use of drugs in this category, such as LSD and psilocybin. Users do not experience withdrawal symptoms, but the general criteria for substance abuse and dependence otherwise apply. Dependence is estimated in approximately 2% of recent-onset users in the United States. Acute hallucinogen intoxication may induce a plethora of physical and psychological effects that can become so overwhelming to the user as to result in seeking emergency psychiatric care. Providing supportive psychotherapy usually proves effective, though sometimes the use of a sedative hypnotic for anxiety is indicated in addition. No randomized controlled trials have examined treatments of hallucinogen abuse or dependence, but standard treatments (motivational interviewing, relapse prevention, outpatient counseling, participation in self-help groups, family therapy) should still be offered.

Role of Pharmacotherapy

Both hallucinogen abuse and hallucinogen dependence are characterized by patterns of compulsive and repeated drug use despite the knowledge of significant harm caused by the activity. However, it is important to point out that hallucinogen use very rarely leads to the development of classic dependence syndromes, such as those seen with opiates or alcohol. As a class, the ▸hallucinogens lack significant direct effect on the dopamine-mediated reward system, and studies to date have failed to train animals to self-administer these compounds as is typical for dependence-inducing drugs (Nichols ▸5). In contrast to the users of other substances of abuse, hallucinogen users do not experience withdrawal symptoms and, therefore, this trait is not a criterion for diagnosing hallucinogen dependence. It should also be noted that, in general, tolerance rapidly increases when hallucinogens are used frequently, and exponentially so with daily use.

Overall rates of abuse and dependence are thought to be low when compared with other substances (Wright et al. ▸10). In the USA, hallucinogen dependence has been estimated in 2% of recent-onset users (first use within 24 months of survey) and 5% of past-onset users (first use 24+ months, last use within 12 months), with a relative risk of dependence apparently greater in users with very early age of onset of hallucinogen use (10–11 years old) (Stone et al. ▸7). These figures are likely to be an overestimate, as the survey included the non-hallucinogenic structured amphetamine methylenedioxymethamphetamine (MDMA) (that does have entactogenic properties) and the dissociative anesthetic PCP within their definition of hallucinogen.

Similar to other substances of abuse, hallucinogens may induce specific, related disorders. These include hallucinogen intoxication, hallucinogen-induced psychotic, mood, anxiety, delirium, or not otherwise specified (NOS) disorder, and the very rare hallucinogen persisting perceptual disorder (HPPD). These disorders arise in the context of substance use and may manifest during intoxication, after the acute effects have subsided, or in the days that follow (APA ▸1). The diagnosis of a hallucinogen-induced psychotic, mood, anxiety, or delirium disorder is made only if the symptoms are in excess of what is expected from intoxication (APA ▸1).

Symptoms, Diagnosis, and Treatment

Hallucinogen ingestion is the central component of hallucinogen abuse and hallucinogen dependence. It is therefore necessary to first discuss the effects, evaluation, and treatment of patients suffering from acute pathological cases of hallucinogen intoxication.

Physical and Psychological Effects of Acute Hallucinogen Intoxication

The typical syndrome of psychological alterations associated with the ingestion of hallucinogens, commonly referred to as "tripping", may induce a wide variety of emotional, cognitive, and behavioral effects (Table ▸1) (Hollister ▸3). The visual components are typically not true hallucinations but illusions, such as the perception of geometric patterns or scenic dream-like visions appearing before closed eyes, perception of movement in stationary objects, and synesthesias. Content of visual and most emotional phenomena typically reflect the psychodynamics of the user (Leuner ▸4). Colors may appear intensified, and altered human and animal forms may appear in the visual field. Hallucinogens activate affectivity and may cause significant changes in mood, where users may change from euphoria to depression or anxiety or vice versa. In some cases, psychotic-like reactions may also be experienced. In short, the psychological effects of hallucinogens are highly variable and strongly influenced by both the individual's mind-set (expectancies and their influence on drug effects), and their physical surroundings and social setting. Toxicity of LSD, psilocybin, and other classical hallucinogens is very low (see Passie et al. ▸6). Overdosing is possible with respect to psychological reactions, but no case of lethal overdose is known, and there is no evidence of long-term neurocognitive toxicity (neurotoxicity) (Halpern and Pope ▸2).

Hallucinogen Abuse and Dependence. Table 1. Hallucinogen[▸a] intoxication may include a cluster of the following.

Physical effects[▸b]	Psychological effects
Typical (mild to very mild): Tachycardia Cardiac palpitation Hypertension or hypotension Diaphoresis Hyperthermia Motor incoordination Tremor Hyperreflexia	Typical: Intensification and lability of affect with euphoria, anxiety, depression and/or cathartic expressions Dream-like state Sensory activation with illusion, ▸pseudohallucination, hallucination, and/or synesthesia Altered experience of time and space Altered body image Increased suggestibility Lassitude/indifference/detachment

(Continued)

Physical effects[▸b]	Psychological effects
Altered neuroendocrine functioning	Acute cognitive alterations with loosening of association, inability for goal-directed thinking, and memory disturbance
Typical (mild to strong): Mydriasis Arousal Insomnia	"Positive": Sense of perceiving deeper layers of the world, oneself, and others ("consciousness expansion") Mystical experience Sense of profound discovery/healing (See ritual uses of psychoactive drugs)
Occasional: Nausea Vomiting Diarrhea Blurred vision Nystagmus Piloerection Salivation	"Negative": Psychosomatic complaint Impaired judgment Derealization Depersonalization Megalomania Impulsivity Odd behavior Paranoid ideation Suicidal ideation

[a]Indolealkylamine and phenylalkylamine hallucinogens only
[b]Some effects are reactionary to psychological content (e.g., increased heart rate and nausea due to anxiety), and complaints can be dependent on factors such as mindset, setting, dose, and supervision. Intoxicated individuals may also deny physical impairment or claim increased energy, sharpened mental acuity, and improved sensory perception

Diagnosis of Acute Hallucinogen Intoxication

Patients present for treatment most often because they experience a panic or depressive reaction, commonly referred to as a "bad trip". Such reactions can begin any time after the onset of effects and may include fears of "going insane" (Strassman ▸8). There may also be paranoid ideation, feelings of being manipulated, or being in a situation without any escape. The acute syndrome of hallucinogen intoxication should be suspected when a patient (or companion) reports recent ingestion of a hallucinogen, and presents with a characteristic constellation of sympathomimetic findings with a clear sensorium (unlike NMDA antagonist dissociative anesthetics like PCP that induce a clouding of consciousness). Since laboratory testing is generally not available in most acute settings, obtaining an accurate history and clin-

ical examination is critical in establishing the diagnosis. Street drugs often contain various adulterants; therefore, the actual identity of the ingested substance may not be known. However, the hallucinogens typically produce similar effects, which should be carefully assessed. Signs and symptoms of hallucinogen intoxication are reviewed in the previous section (see Table ▸1). Physical examination will also provide important clues that can support the diagnosis of hallucinogen intoxication (in particular, widely dilated pupils that do not rapidly/tightly constrict to accommodate bright light). Hallucinogens have varying duration of action; nevertheless, the acute reaction typically lasts less than 10 h (maximum 12–24 h), and reactions lasting longer will require further investigation to rule out other etiologies.

Treatment of Acute Hallucinogen Intoxication

The "talk down" (more accurately the "talk through") is usually the primary effective intervention indicated in these situations (Taylor et al. ▸9). This consists of keeping the patient in a low-stimulus environment (i.e., a quiet space with dimmed lights and minimal distractions) and providing emotional support. Arranging for a reliable sitter (a non-intoxicated companion) to look after the patient is recommended. The sitter can help in keeping the patient calm and oriented by providing a sympathetic presence. In addition, the sitter can also provide reassurance to the patient that the experience is generally non-hazardous, drug-induced, and time-limited, which will resolve with full recovery. The patient should not be left alone until the effects of the drug wear off.

If severe agitation does not respond to redirection and concerns for safety of the patient or others remain, benzodiazepines are quite effective in reducing anxiety and panic. Many authorities recommend oral diazepam or lorazepam, although intramuscular and intravenous routes are more immediately effective. Avoid physical restraints if possible and limit the use of antipsychotics since paradoxical effects have been reported (Strassman ▸8). While no controlled trials have examined the efficacy of antipsychotic drugs for hallucinogen-induced agitation, rare cases may require such an intervention after benzodiazepines have not proven sufficient. However, great caution must be exercised, since first generation antipsychotics lower the seizure threshold and may also induce hypotension.

Once the acute symptoms subside, patients are usually able to go home accompanied by a companion (Strassman ▸8). It is important to advise patients that subsequent ingestion of hallucinogens may precipitate similar reactions. If symptoms persist for longer than 24 h or there are accompanying severe mood or psychotic symptoms that warrant independent clinical attention, hospitalization may be considered.

Gastric lavage should be avoided as it is not effective in removing substances that were usually ingested several hours prior to hospital presentation. Moreover, gastric lavage will invariably worsen the patient's mental state.

Diagnosis of Hallucinogen Abuse and Dependence

Multiple drug use is common; the differential must always contain other substance use or substance-induced disorders. Alcohol abuse and dependence frequently occurs comorbid to hallucinogen abuse and should therefore also be assessed carefully in this population. ▸Schizophrenia, schizophreniform, bipolar, and schizoaffective disorders must also be ruled out in these patients by assessing the longitudinal course of the symptom constellation and their temporal relation to hallucinogen ingestion.

Treatment of Hallucinogen Abuse and Dependence

There are no randomized controlled trials that have examined the treatment of hallucinogen abuse or dependence. However, general principles that apply to other substances of abuse should be employed in treating these patients. Motivational interviewing, detoxification, relapse prevention, intensive outpatient counseling, involvement with self-help groups, and family therapies are examples of interventions that need to be individualized for each particular patient.

Since polysubstance abuse and dependence is common, treatment should also target other substance abuse and dependence that are thought to be contributing to the disturbances. Furthermore, treatment should be provided with a dual diagnosis approach, and any underlying psychiatric disorder should be treated concurrently. No controlled trials have been conducted to evaluate the efficacy of pharmacotherapies.

Cross-References

▸Dissociative Anesthetics
▸Hallucinogens
▸Schizoaffective Disorder
▸Schizophrenia

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Hallucinogens

▸Hallucinogen Abuse and Dependence
▸Schizophrenia

Haloperidol

Definition

Antipsychotic drug of the older, first generation category (mainly dopamine D2 receptor blocker/antagonist).

Cross-References

▸Antipsychotic Drugs
▸First-Generation Antipsychotics

Hypometria

Definition

An undershoot in saccade amplitude, that occurs most acutely for internally generated saccades, often observed in patients with Parkinson's disease or medicated patients with schizophrenia.

Intramuscular Antipsychotics

Cross-References

▸Depot Antipsychotics
▸Schizophrenia
▸Second and Third Generation Antipychotics

Isolation Rearing

Definition

An animal model in which rats, immediately after weaning (usually postnatal day 21), are housed in isolation from siblings for an extended period (usually several weeks). In adulthood, these animals show many characteristics also seen in patients with schizophrenia.

Cross-References

▸Animal Models for Psychiatric States

K-Hole

Definition

The term "K-hole" is a slang term for a state of dissociation occurring when large doses of ketamine are ingested. These effects, which mimic the schizophenic symptoms, result in the user feeling trapped in a state in which they may feel detached from their bodies and unable to move. Other symptoms include distortion of the senses, particularly vision, result in disorientation, and can cause nausea and vomiting. Distortions in bodily awareness, perceptions of falling and flying, and intense hallucinations may also be experienced. The combination of these effects leave the user feeling trapped in a frozen state, as if stuck in a hole peering out.

Cross-References

▸Dissociative Anesthetics

Long acting antipsychotics

Cross-References

▸Depot Antipsychotics
▸Schizophrenia
▸Second and Third Generation Antipychotics

Lurasidone

Definition

Lurasidone is a full antagonist at D2 and $5HT_{2A}$ receptors which also has affinity to $5HT_7$ and $5HT_{1A}$ receptors. It is a 2^{nd} generation antipsychotic recently approved by the FDA.

Cross-References

▸Second- and third-generation antipsychotics

Major Tranquilizer

Synonyms
Antipsychotic
Neuroleptics

Definition
A medication used in the treatment of psychotic disorders of any type with a particular emphasis on inducing sedation. The term is less used than its synonyms and is poorly characterized in pharmacological terms. It tends to be used less by psychiatrists than by nonspecialists.

Cross-References
- ▸Antipsychotic Drugs
- ▸First-Generation Antipsychotics
- ▸Second and Third Generation Antipsychotics

Maternal Deprivation Model

Definition
An animal model in which young rats are separated from their mother for a single period of 24 h. The optimal day for separation is postnatal day 9. These animals develop a large number of schizophrenia-like phenomena in adulthood. Interestingly, most of these phenomena occur after puberty in accordance with the clinical literature on schizophrenia.

MATRICS

Synonyms
Measurement and treatment research to improve cognition in schizophrenia

Definition
This is an initiative of the National Institutes of Health in the USA to enhance the methodology of assessing cognitive impairment in ▸schizophrenia, using neuropsychological tests, for the purpose of clinical trials. This initiative has also boosted interest in cognitive assessment in experimental animals in order to evaluate putative cognitive enhancing compounds.

Methamphetamine

Synonyms

Desoxyephedrine
Methylamphetamine
N-methylamphetamine

Definition

Methamphetamine is a psychostimulant and sympathomimetic drug that has a blood half-life of 9–15 h. The primary metabolite of methamphetamine is amphetamine, a chemical that itself is a potent psychostimulant. Methamphetamine is clinically available for the treatment of obesity, narcolepsy, and in some cases ADHD. Methamphetamine is a highly potent drug of abuse, with its illicit use reaching epidemic proportions in several Western countries including North American, Asian, and Pacific regions. Chronic exposure to methamphetamine can lead to schizophrenia-like psychosis and neurotoxic degeneration of dopaminergic neurons.

Cross-References

▸Dopamine

Moperone

Definition

Moperone is a first-generation (typical) antipsychotic drug that belongs to the butyrophenone type approved in Japan for the treatment of ▸schizophrenia. It has higher antagonist affinity for D2- than 5-HT2A-receptors. It also has high binding affinity for sigma receptors. It can induce extrapyramidal motor side effects, insomnia, and thirst, but it displays generally low toxicity.

Cross-References

▸Butyrophenones
▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics

Mosapramine

Synonyms
Y-516

Definition
Mosapramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class approved in Japan for the treatment of schizophrenia. It is a potent dopamine antagonist with high affinity for D2, D3, and D4 receptors, but lower affinity for 5-HT2A-receptors. It can induce extrapyramidal motor side effects and drowsiness, but it displays generally low toxicity.

Cross-References
▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics
▸Schizophrenia

Negative Symptoms Syndrome

Synonyms
Deficit symptoms syndrome

Definition
A syndrome that involves the lacking of a number of mental features or capacities that would be expected to be present in a healthy individual. These features and capacities include: the ability to sustain an adequate level of attention during tasks, activities, or social encounters; a full range of genuine, appropriately responsive, and appropriately sustained affect; an adequate quantity of spontaneous speech that contains objective content and that is delivered without disruptive delays in either initiating or sustaining the speech; an appropriate level of attention and caring concerning grooming and personal hygiene; an appropriate level of motivation and persistence concerning work, school, or other productive activities; an appropriate level of energy for initiating and sustaining activities, and capacity for self-starting and self-direction; an appropriate level of interest and investment in, and pleasure derived from, enjoyable or recreational activities; and an age-appropriate interest in, and capacity for, friendship, cooperation, and interpersonal closeness or intimacy.

Nemonapride

Definition
Nemonapride is a first-generation (typical) antipsychotic drug that belongs to the benzamide class approved in Japan for the treatment of schizophrenia. It is a potent dopamine antagonist with high affinity for D2, D3, and D4 receptors. In addition, it is a potent 5-HT1A receptor agonist and has relatively high affinity for sigma receptors, with little affinity for 5-HT2A receptors. It can induce extrapyramidal motor side effects and has a propensity to elevate prolactin secretion, but it displays generally low toxicity.

Cross-References
▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics
▸Schizophrenia

Neurodevelopmental Hypothesis

Definition

The neurodevelopmental hypothesis suggests that ▸schizophrenia results from abnormalities in neuronal connectivity, which arise during fetal life but are not expressed until the onset of illness.

Neurotoxicity and Schizophrenia

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Definition

Neurotoxicity is the tendency of substances (also called neurotoxins), conditions, or states to alter the normal activity of the nervous system. This can eventually disrupt or even kill neurons; key cells that transfer and process signals in the brain and parts of the nervous system. Neurotoxicity can result from exposure to drug therapies and certain drug (ab-)use.

The "neurotoxicity theory" of ▸schizophrenia states that an (untreated) psychosis is neurotoxic to the brain and that brain changes are an inherent feature of the neurobiological disease process in schizophrenia. Although the pathophysiology of this disorder is still unknown, we do know that antipsychotics; (dopamine receptor blockers), reduce symptoms of schizophrenia, but that party drugs like cocaine and amphetamine increase dopamine in the brain and may induce psychosis.

The term *neurotoxic* is used to describe a substance, condition, or state that damages the nervous system and/or brain, usually by killing neurons. The term is generally used to describe a condition or substance that has been shown to result in observable physical damage.

Current Concepts and State of Knowledge

Introduction

Although Kraepelin (▸12) suggested that ▸schizophrenia, dementia praecox, was a chronic, deteriorating psychotic disorder, evidence was lacking to prove this; in postmortem studies, no or little abnormalities in brains of patients with schizophrenia were found. In the 1960s and 1970s, schizo-

phrenia was not thought to be a brain disease at all. Clinical investigators considered failing-family interactions instead as a cause. Especially, failing mother–child interaction was thought to cause or worsen schizophrenia.
This all changed when new in vivo neuroimaging techniques, such as Computer Tomography (CT) in 1976 revealed that patients with schizophrenia had enlarged ventricles when compared with a group of age-matched controls (Johnstone et al. ▸11). In the early 1900s, the first evidence of brain ventricular enlargement was already provided by a pneumoencephalography (PEG) study in a small sample of schizophrenia patients (Jacobi and Winkler ▸9).
Because of the lack of progression of cerebral ventricular enlargement of the earlier studies, the ▸neurodevelopmental hypothesis began to emerge by which schizophrenia is suggested to result from abnormalities in neuronal connectivity, which arise during fetal life but are not expressed until the onset of illness. Despite the evidences in favor of the neurodevelopmental hypothesis, such as delayed milestones, there are some substantial symptoms of schizophrenia that cannot be explained with the neurodevelopmental hypothesis. The apparent progression of clinical aspects of the syndrome in some patients, including deterioration, dilapidation, and treatment resistance may suggest that schizophrenia is a progressive illness. Furthermore, recent longitudinal magnetic resonance imaging (MRI) studies in patients with schizophrenia have shown that through the course of the illness the brain volume reduces progressively. It remains unclear what the underlying neuropathological mechanisms are causing these progressive brain volume changes in schizophrenia, but it is thought that psychosis could be neurotoxic.
This essay will briefly describe the scientific evidence in favor of schizophrenia being a progressive brain disease. It will then discuss the neurotoxicity hypothesis of schizophrenia and the concept of neuroprotection.

Neuroimaging Studies

In 1976, a new in vivo neuroimaging technique, CT was first used in schizophrenia research by Johnstone et al. (▸11). In this study, patients with schizophrenia showed enlarged ventricle volumes when compared with age-related healthy control subjects. In the last two decades, numerous studies were conducted using MRI techniques. In 2000, a cross-sectional meta-analysis (Wright et al. ▸22) convincingly showed that brain volume changes are present in schizophrenia. Lateral ventricle volume was found to be increased (16%) while cerebral volume was reduced (2%). The latter was primarily attributed to a decrease in gray matter volume (2%). Nevertheless, a small but significant reduction was found in white matter volume (1%). Furthermore, the improved quality of the MRI scans made it also

possible to manually delineate brain areas of interest. Regional pathology indicates larger reductions in temporal and frontal lobe and more specifically in medial temporal structures (hippocampus and amygdala). The finding of reduction in frontal and (medial) temporal areas of the brain in patients with schizophrenia has been corroborated by using a voxel-based morphometry approach.

It has long been argued that the brain volume changes found in schizophrenia are (partly) caused by the antipsychotic medication. Indeed, in the early stages of schizophrenia progressive decreases in gray matter (Cahn et al. ▸1) and frontal lobe volume (Gur et al. ▸6; Madsen et al. ▸17) have been found associated with the amount of antipsychotic medication taken. Those patients who were prescribed the highest doses of antipsychotic medication also had the greatest progressive decreases in brain volumes. Nevertheless, this brain volume decrease might not be a direct effect of the medication as those who are prescribed the highest doses of antipsychotic medication are generally the most severely ill patients. Increases and decreases in brain volumes depend on the type of antipsychotic medication. Basal ganglia volumes decrease on typical antipsychotic medication and increase (or normalize) on atypical medication or ▸clozapine (Hakos et al. ▸7; Scheepers et al. ▸20). Recent longitudinal MRI studies have shown that ▸olanzapine and ▸clozapine actually attenuates brain tissue loss in schizophrenia, whereas typical antipsychotic medication do not (DeLisi ▸4; Lieberman et al. ▸16; van Haren et al. ▸21).

In the last decade, many studies have focused their attention on investigating the effects of first psychotic episode on the brain. Studying the early phase of the illness is useful since the confounding effects of chronicity and long-term medication can be excluded. MRI studies in antipsychotic naïve patients appear to show a relative paucity of ▸brain abnormalities which stands in marked contrast with findings in more chronic schizophrenia patients. Several explanations can be contemplated to elucidate the discrepancy in brain abnormalities between those patients who are chronically ill and those who are in the early phase of the illness. Medication might increase brain abnormalities and could contribute to these brain volume changes. Finding few brain abnormalities in antipsychotic naïve patients with schizophrenia could also be the result of a selection bias favoring the inclusion of patients who have a less severe form of schizophrenia; and last but not least, progression of the illness may lead to an increase of brain abnormalities.

Indeed, there is a growing body of evidence that brain abnormalities become greater in schizophrenia over the course of the illness. Various reviews of (longitudinal) MRI studies in patients with (first-episode) schizophrenia

conclude that there is accelerated loss of gray matter particularly in the frontotemporal cortical areas, as well as sulcal and ventricular expansion over time. In schizophrenia, a 3% gray-matter decrease is found with a 0.5% decrease per year, which is consistent with the result of postmortem studies in schizophrenia (Hulshoff Pol and Kahn, ▸8). Although changes in brain volume over time are reported in both first-episode patients and chronic patients with schizophrenia, the magnitude in first-episode patients (e.g., −1.2% in 1 year for whole brain volume) suggest that these brain volume reductions are particularly prominent during the first years of illness (Cahn et al. ▸1).

Nevertheless (progressive), brain-volume reductions are only relevant if they are associated to the clinical characteristics and outcome in schizophrenia. The most consistent finding of longitudinal MRI studies in first-episode and chronic schizophrenia is the relationship between reduced brain volume (gray matter decrements and ventricular increments) and poor outcome. Psychotic symptoms have also been examined in relation to brain-volume loss over time. A recent MRI study investigated the relationship between psychosis and brain-volume change in first-episode patients with schizophrenia over the first 5 years of illness. Associations between gray-matter volume loss, lateral and third ventricle volume increase, and longer duration of psychosis were found. Total duration of psychotic symptoms was further associated with greater decreases in total brain and cerebellar volume (Cahn et al. ▸2). Other MRI studies, which examined smaller brain structures found reduced volumes of the medial temporal lobe, superior temporal gyrus, and hippocampal volumes in patients with psychotic symptoms. Furthermore, a long duration of untreated psychosis (DUP) is associated with poor clinical and social outcome. Various research groups have now found that patients with a longer DUP have more decreased gray matter volume than patients with a shorter DUP (Lappin et al. ▸13). These findings suggest that brain-volume loss over time could be attributable to the "toxic" effects of the psychotic state.

Nevertheless, besides the (untreated) psychosis, there are other factors that could be neurotoxic in schizophrenia, such as cannabis use and stress. About 28–50% of patients with schizophrenia use cannabis. Clinically, patients who use cannabis have more positive (but not negative) symptoms, an earlier disease onset and an increased number of psychotic episodes when compared with patients who do not use cannabis. Rais et al. (▸18) found significantly more decrease in brain volume in patients using cannabis when compared with nonusing patients over a 5-year period.

Until now, there is only indirect evidence that life events might affect brain volumes in schizophrenia, as lower gray- and white-matter volumes in

schizophrenia are associated with a dysregulated dopaminergic/ noradrenergic-mediated stress response.

Neurotoxicity

The neurotoxicity theory of schizophrenia states that an (untreated) psychosis is neurotoxic to the brain and that brain changes are an inherent feature of the neurobiological disease process in schizophrenia. As mentioned previously, MRI studies show volume reductions over time, particularly of gray matter. Nevertheless, the brains of schizophrenia patients do not reveal characteristic histopathology like other neurodegenerative diseases do. Moreover, postmortem studies have not found evidence of neuronal injury or degeneration. A neurodegenerative process in the brain normally accompanies loss of neuronal cells and microglial cells (a type of glial cells that are the resident macrophages of the brain).

In schizophrenia, a lack of microglial cells has been found. Some researchers have postulated that neuronal cell death occurs in schizophrenia, but that this cell death is programmed (apoptosis) instead of necrosis, where microglial cells "eat" the injured cells and leave scar tissue at the place where the necrotic cell used to be. Various intracellular and extracellular events, like increased glutamate stimulation, can induce a programmed apoptotic cascade which results in cell destruction. This apoptotic cascade could then produce synapse loss and synaptic remodeling, and would compromise cell function and alter brain morphology (Lieberman ▸14).

Postmortem studies in schizophrenia have also reported reduced dendritic spines; a measure of the amount of synaptic contacts between neurons. Furthermore, they found smaller dendritic arbors on the pyramidal cells of the cortex, damage to myelinated fiber tracts, and increased neuronal density because of reduced neuropil; the synaptic syncytium between neurons where synaptic connections are formed between branches of axons and dendrites (Davis et al. ▸3). This decreased interneuronal neuropil could cause functional and anatomic hypoconnectivity in a schizophrenic brain and would explain the decreased cortical volumes as seen on MRI (Davis et al. ▸3).

Thus, a higher concentration of neurotransmitters in the brain can lead to excitotoxication and could induce cell death which in turn could result in brain-volume reduction. Although the pathophysiology of schizophrenia is still unknown, we do know that antipsychotics, dopamine receptor blockers, reduce symptoms of schizophrenia, and that party drugs like cocaine and amphetamine increase dopamine in the brain and may induce psychosis. So, it is thought that in schizophrenia there is an increase in dopamine in the mesolimbic system. This is the so-called ▸dopamine hypothesis of schizophrenia. Nevertheless, this hypothesis only explains the positive symptoms

and does not explain the negative and cognitive problems seen in schizophrenia (aminergic hypotheses of schizophrenia). ▸Phencyclidine (PCP), an *N*-methyl d-aspartate (NMDA)-receptor (a glutamate receptor) antagonist, which disinhibits excitatory glutamatergic pathways causing neuronal damage, induces symptoms more similar to those seen in schizophrenia. The glutamate hypothesis of schizophrenia postulates that there is a hypofunction of the NMDA receptor in the schizophrenic brain. The reduced activity of the NMDA-receptor affects the glutamate concentration, but influences other neurotransmitter systems, such as dopamine and GABA in the brain.

The NMDA receptor is an ionotropic excitatory receptor with glutamate as its ligand. Binding of glutamate causes an influx of Na^+ and $Ca2^+$ and thereby, postsynaptic membrane depolarization. When there is a reduced amount of NMDA receptors, the excess of glutamate stays in the synaptic cleft and increases stimulation of other ionotropic receptors like those for α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainite receptors. This overstimulation, also called excitotoxication, leads to dysregulation of the $Ca2^+$ homeostasis and causes oxidative stress and thereby, apoptosis (Deutsch et al. ▸5).

Antagonism, or reduced activity, of the NMDA receptor and thus a hypofunctioning of glutamate signaling may also result in changed dopamine concentration. Prefrontal D1 receptors are hypostimulated, which may lead to negative and cognitive symptoms of schizophrenia. A later developed episodic hyperactivity of the mesolimbic dopamine system may lead to positive symptoms of schizophrenia (Jarskog et al. ▸10).

The NMDA receptors are also present at the GABAergic inhibitory interneurons within the cortex. Glutamate activation normally leads to the release of GABA to inhibit glutamatergic neurons and the release of glutamate. With reduced NMDA-receptor activity, a decreased amount of GABA will inhibit glutamate activity and thereby cause a heightened activity of glutamatergic neurons. GABAergic inhibition is of great importance in critical circuits of normal brain function and could be the cause of the cognitive symptoms in patients (Reynolds et al. ▸19).

Neuroprotection

Neuroprotection refers to treatment that helps to maintain the functional integrity of the brain in response to neurobiological stress, such as apoptosis and less synaptic activity due to neurotoxicity. Neuroprotection is already a rapidly advancing concept in the treatment of neurological disorders. Moreover, it is also seen as a therapeutic treatment for psychiatric disorders to improve loss of function or prevent neurodegeneration from occurring. The most common treatment for schizophrenia is antipsychotic medica-

tion. Almost all patients with schizophrenia receive antipsychotic medication during their illness; therefore, it is not clear whether the progressive brain changes occurring in the brains of the patients are due to the illness itself (untreated psychosis) or perhaps due to the use of antipsychotic medication. In other words: Are antipsychotics neurotoxic or neuroprotective to the brain (Hulshoff Pol and Kahn ▸8)?

Increases and decreases in brain volumes appear to depend on the type of antipsychotic medication. Basal-ganglia volumes decrease on typical antipsychotic medication and increase (or normalize) on atypical medication or clozapine. Recent longitudinal MRI studies have shown that olanzapine and clozapine actually attenuates brain-tissue loss in schizophrenia, whereas typical antipsychotic medication does not. It has been suggested that antipsychotic drugs, specifically the atypicals, have an effect on synaptic remodeling and neurogenesis, and thereby ameliorate the pathophysiology of schizophrenia (Lieberman et al. ▸15). The progressive brain loss seen in patients who are treated with ▸haloperidol and other typical antipsychotics could be due to the fact that typical antipsychotics are not neuroprotective, and thus, the progressive brain loss continues to increase despite the treatment.

Furthermore, it has been suggested that physical exercise, psychoeducation, and cognitive therapy in schizophrenia are neuroprotective, but very limited research has been done so far. Future studies need to be conducted to examine the neuroprotective effects of medication and (psychosocial) treatments in schizophrenia.

Cross-References

▸Antipsychotic Medication: Future Prospects
▸First-Generation Antipsychotics
▸Schizophrenia

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New Generation Antipsychotics

Cross-References

▸Second- and third-generation antipsychotics

Nucleus Accumbens

Synonyms

NAcc

Definition

The *nucleus accumbens* is a small brain region located in the ventral striatum. It is a major projection area (terminal field) for dopaminergic neurons located in the ventral tegmental area of the midbrain. It is thought to play an important role in many behavioral and psychological processes, including reward-related behavior, incentive motivation, memory processing and

habit formation, and in dopamine-mediated psychotic symptoms in ▸schizophrenia. It has been implicated in the reinforcing effects produced by various natural stimuli such as food, water, and sexual opportunity, as well as by drugs of abuse. In addition, it receives projections from the prefrontal cortex that may mediate the impulsivity associated with compulsive drug taking.

Olanzapine

Definition

Antipsychotic drug of the second generation, atypical category with combined dopamine D2/serotonin2 receptor blocking properties.

Cross-References

▸Second and Third Generation Antipsychotics

Paliperidone

Synonyms
9-hydroxyrisperidone

Definition
Paliperidone is a second-generation antipsychotic medication indicated for the acute and maintenance treatment of schizophrenia. It acts as a dopamine D2 and serotonin 5-HT2A antagonist. It is the 9-hydroxymetabolite of risperidone with which it shares many pharmacological properties. An extended release formulation of paliperidone allows for once-daily dosing, results in lower peak plasma levels, and thereby limits the need for dose-titration that is otherwise required at the start of treatment with risperidone.

Cross-References
▸Antipsychotic Medication: Future Prospects
▸Risperidone
▸Schizophrenia
▸Second and Third Generation Antipsychotics

PANSS

Synonyms
Positive and negative syndrome scale

Definition
PANSS is a scale for the measurement of positive, negative, and general schizophrenic symptoms.

Partial Agonist

Definition
Partial agonists bind to and activate a receptor, but are not able to elicit the maximum possible response that is produced by full *agonists*. The maximum response produced by a partial agonist is called its intrinsic activity and may be expressed on a percentage scale where a full agonist produced a 100% response. A key property of partial agonists is that they display both agonistic and antagonistic effects. In the presence of a full agonist , a *partial agonist* will act as an antagonist, competing with the full *agonist* for the

same receptor and thereby reducing the ability of the full agonist to produce its maximum effect. The balance of activity between agonist and antagonist effects varies from one substance to another, according to their intrinsic activities, and is also influenced by the test system used to measure their effects. Weak partial agonists are those compounds, possessing low intrinsic activity, that are able to produce only a small percentage of the total response produced by an agonist and which act predominantly as antagonists. Strong partial agonists may come close to mimicking the maximum effects of a full agonist and may display only weak antagonistic ability. When the test system under study has a large receptor reserve, weak partial agonists show greater agonist activity then when the system has a small receptor reserve.

Pediatric Schizophrenia

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Synonyms

Childhood-onset schizophrenia
EOS
Early onset schizophrenia
Schizophrenia with onset during childhood and adolescence
Very early onset schizophrenia (VEOS)

Definition

The onset of ▸schizophrenia before age 18 years, i.e., during childhood and adolescence. Early onset schizophrenia refers to cases with onset between age 13 and 17 years whereas very early onset schizophrenia or childhood-onset schizophrenia refers to onset before age 13 years.

Role of Pharmacotherapy

Nosology, Epidemiology, Phenomenology

The diagnosis of pediatric schizophrenia is made using unmodified criteria for adulthood-onset schizophrenia (i.e., onset at age 18 or older). The subtypes of schizophrenia are also identical in both groups. While the prevalence of childhood-onset schizophrenia (onset of psychotic symptoms before 13 years of age) is very low (approximately 1/100 cases of schizophrenia), approximately 12%–33% of individuals with schizophrenia have their illness onset between age 13 and 17 (Kumra et al. ▸6). Current phe-

nomenological, cognitive, genetic, and neuroimaging data strongly support continuity between pediatric and adult onset schizophrenia, suggesting similar neurobiological correlates and clinical deficits (Kyriakopoulos and Frangou ▸7). Although the (yet unknown) etiology and pathophysiology of pediatric and adulthood schizophrenia are believed to be very similar, patients with pediatric onset schizophrenia seem to have a worse illness course that generally is characterized by greater chronicity and functional impairment compared to the adulthood-onset counterpart (Kumra et al. ▸6). Whether this is related to direct biological effects or to the fact that the psychotic illness occurs at a time of critical developmental tasks, which disrupts the achievement of educational and social milestones, is unclear. However, due to the difference in outcomes, schizophrenia with onset before 18 years has been used as a distinct phenotype for genetic research in order to achieve greater homogeneity. Of note, however, patients with adulthood-onset schizophrenia also commonly experience varying degrees of developmental delays, psychosocial and educational problems, and functional decline during childhood or adolescence. Moreover, patients with pediatric and adulthood-onset schizophrenia frequently report "prodromal" psychotic symptoms and signs in childhood or adolescence. The ▸schizophrenia prodrome often consists of depressive and negative symptoms as well as, attenuated psychotic symptoms (i.e., subthreshold forms of unusual ideas, suspiciousness, grandiosity, abnormal perceptions, and disorganized thought, speech or behavior) (Correll et al. ▸4).

The Evidence Base

To date, 14 randomized controlled trials (RCTs) (n = 1,155) have been completed in patients with pediatric schizophrenia (Kumra et al. ▸6; Sikich et al. ▸10). Six trials had a placebo comparator and evaluated the efficacy and safety of ▸haloperidol (N = 1, n = 12), haloperidol and loxapine (N = 1, n = 75), ▸aripiprazole (N = 1, n = 301), quetiapine (N = 1, n = 220), ▸risperidone (N = 1, n = 160), and ▸olanzapine (N = 1, n = 107), and one trial (n = 279) used a very low dose of risperidone (0.15–0.6 mg/day) as a pseudo-placebo comparator (N denotes the number of trials with each drug, n denotes the number of patients).

In addition to the placebo-controlled, three-arm study comparing haloperidol and loxapine (N = 1, n = 75), another seven trials (n = 275) compared antipsychotics head-to-head in youth with schizophrenia. These included a comparison of ▸thiothixene and ▸thioridazine (N = 1, n = 21), haloperidol, olanzapine, and risperidone (N = 1, n = 50, 52% schizophrenia spectrum psychosis, 48% affective spectrum psychosis), molindone, olanzapine, and risperidone (N = 1, n = 119), haloperidol and ▸clozapine (N = 1, n = 21),

clozapine and olanzapine ($N = 2$, $n = 64$), and olanzapine and ▸quetiapine ($N = 1$, $n = 50$, 64% schizophrenia spectrum psychosis, 36% affective spectrum psychosis).

Efficacy

While the two underpowered studies from 1976 and 1984 involving ▸first-generation antipsychotics (FGAs) did not significantly separate from placebo, there was a trend for greater improvement on the Clinical Global Impressions-Severity (CGI-S) scale in favor of haloperidol and loxapine in the one study, and a significant baseline to endpoint change in the Brief Psychiatric Rating Scale (BPRS) for haloperidol, but not for placebo (Kumra et al. ▸6). By contrast, all of the second-generation antipsychotic (SGA) trials completed since 2005 showed significantly greater improvements on the primary outcome measure, the Positive and Negative Syndrome Scale (PANSS) for all doses that were studied. Overall, the numbers-needed-to-treat (NNT) for study defined response for aripiprazole, olanzapine, quetiapine, and risperidone range from 4 to 10. Based on the results from these placebo-controlled trials in pediatric schizophrenia, risperidone, quetiapine, olanzapine and aripiprazole were approved by the Food and Drug Administration (FDA) in the USA for use in adolescents age 13–17 years old, and aripiprazole was approved for use in adolescents age 15–17 years in Europe by the European Medicines Agency (EMEA). Moreover, after an official FDA hearing in June 2009, olanzapine and quetiapine are expected to receive FDA approval in the USA for use in adolescents age 13–17 years with schizophrenia. Despite inadequate trial data for first-generation antipsychotics, haloperidol and thioridazine were grandfathered in, being indicated for adolescents with schizophrenia in the USA, and the dosing and use of several first-generation antipsychotics, mainly haloperidol, for adolescents with schizophrenia is mentioned in regulatory documents in some European countries.

Across the seven studies, comparing two FGAs, one FGA with one or two SGAs, or two SGAs with each other, the only significant group differences were found in favor of clozapine compared to haloperidol, regular dose olanzapine (up to 20 mg/day) and to "high"-dose olanzapine (10–30 mg/day) (Kumra et al. ▸6; Sikich ▸10). Since in all active controlled studies, the numbers of patients in individual study arms were very small, ranging from 8 to 41, a type-2 error cannot be excluded; yet the results of relatively similar efficacy results parallel data in adult schizophrenia.

Tolerability and Side Effects

Children and adolescents seem to be more sensitive to most antipsychotic adverse effects, including sedation, Extrapyramidal motor side-effects (ex-

cept for ▸akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain, and metabolic abnormalities (Correll ▸1). On the other hand, adverse effects that require a longer time to develop (e.g., diabetes mellitus) and that are related to greater medication dose and lifetime exposure (e.g., ▸tardive dyskinesia) are less prevalent in pediatric samples. However, there is concern that these later onset adverse events are not seen because of short follow-up periods and that they may emerge in vulnerable patients prematurely in adulthood the earlier antipsychotics are started in childhood.

Extrapyramidal Side Effects Extrapyramidal Side Effects (EPS)

In general, children and adolescents are more sensitive than adults to Parkinsonian side effects associated with FGAs and SGAs (Correll ▸1). An RCT of 40 youths with psychotic disorders comparing haloperidol (mean dose: 5 mg/d), risperidone (mean dose: 4 mg/d), and olanzapine (mean dose: 12 mg/d) found substantial EPS not only with haloperidol (67%), but also with olanzapine (56%) and risperidone (53%), although haloperidol-treated patients reported more severe EPS (Sikich et al. ▸9). In the Treatment of Early-Onset Schizophrenia-Spectrum (TEOSS) study, patients randomized to molindone (mean dose: 59.9 mg/day) required more frequent coadministration of an anticholinergic (45%) than patients randomized to risperidone (mean dose: 2.9 mg/day, 34%) or olanzapine (mean dose: 11.8 mg/day, 14%), even though patients on molindone were given prophylactic, blinded benztropine 0.5 mg bid (Sikich et al. ▸10). Clozapine and quetiapine appear to be associated with relatively low EPS rates in pediatric patients. For aripiprazole and ▸ziprasidone, EPS rates appear to increase with increasing dose.

Akathisia

Incidence rates of ▸akathisia from placebo-controlled RCTs in pediatric schizophrenia have been reported for aripiprazole (5% for placebo, 5% in the 10 mg/day group, and 11.8% in the 30 mg/day group), risperidone (6% on placebo, 7% in the 1–3 mg/day group, and 10% in the 4–6 mg/day group), corresponding to NNH of 15 to no risk for aripiprazole 30 mg/day and 10 mg/day, respectively, and 25 to 100 for risperidone 4–6 mg/day and 1–3 mg/day, respectively (Correll ▸2). The relatively high akathisia rates for placebo, especially in the pediatric schizophrenia trials, suggest the potential presence of a relevant carryover effect from prior antipsychotic treatment or the possibility of withdrawal phenomena after a brief washout from antipsychotics and/or medications that can mitigate akathisia. In the TEOSS study, molindone, but not olanzapine or risperidone, was associated with a significantly greater rate of self-reported akathisia compared to risperidone and olanzapine (Sikich et al. ▸10).

Withdrawal Dyskinesia

During FGA treatment, youths are at risk of developing withdrawal dyskinesia, yet, unlike in adults, dyskinetic movements are frequently reversible. Withdrawal dyskinesia rates appear to be lower with SGAs compared to FGAs, although a switch from an antipsychotic with strong D2 affinity (risperidone or aripiprazole) to one with less potent affinity (quetiapine or clozapine) may predispose to withdrawal dyskinesia (Correll ▸1).

Tardive Dyskinesia Tardive Dyskinesia (TD)

Long-term TD data in patients with pediatric schizophrenia are lacking. A meta-analysis of 10 studies lasting at least 11 months reported on TD rates in 783 patients age 4–18 (weighted mean: 10) years old. Most patients were prepubertal (80%), male (82%), white (79%), and only 3% had a schizophrenia spectrum disorder (Correll and Kane ▸3). Across these studies, only three cases of TD were reported, resulting in an annualized incidence rate of 0.4%, which was approximately half of the rate found in a prior meta-analysis of TD rates in adults. However, it is unclear how much these data can be extrapolated to pediatric patients with schizophrenia, as antipsychotic doses were low, and lifetime exposure was relatively short.

Weight Gain

Although pediatric data are still limited, youth with severe psychiatric disorders seem to be at increased risk for being overweight or obese, especially when exposed to antipsychotics for longer periods of time. Age-inappropriate weight gain is of particular concern in pediatric patients, due to its association with glucose and lipid abnormalities and cardiovascular morbidity/mortality. Reasons for weight gain are complex, including psychiatric illness, unhealthy lifestyle, and treatment effects. A review of pediatric data suggests that the weight gain potential of FGAs and SGAs follows roughly the same ranking order as found in adults, but that the magnitude is greater (Correll ▸1). Exceptions may be a greater relative weight gain propensity of risperidone, and a greater likelihood of aripiprazole and ziprasidone to not be weight neutral in subgroups of pediatric patients (Correll et al. ▸5). For example, in an 8-week study, Sikich et al (▸9) found a higher weight gain in young patients age 5–17 years with psychotic disorders taking olanzapine for 8 weeks (7.1±4.1 kg) than in those taking either risperidone (4.9±3.6 kg) or haloperidol (3.5±3.7 kg); all weight gain was severe and disproportionate to that expected from normal growth. Results from four 6-week studies in adolescents with schizophrenia suggest that the olanzapine group had the greatest risk for significant weight, risperidone and quetiapine were associated with intermediate risk, and aripiprazole showed the lowest risk. The respective numbers-needed-to-harm (NNH) for ≥7% weight gain was 4 for

olanzapine, 7–8 for quetiapine, 8 for risperidone, and 25–34 for aripiprazole (Correll ▸2). However, the interpretation of weight gain results across various studies and agents is complicated by the effects of baseline weight, developmental stage and growth, past antipsychotic exposure, treatment duration and setting, comedications, etc., that varied across trials.

Metabolic Adverse Effects

Whereas in adults the link between antipsychotics and adverse metabolic effects, such as dyslipidemia, hyperglycemia, diabetes, and metabolic syndrome, has been established, the few pediatric studies which reported data have produced mostly negative results. Interpretation of these findings is limited by the small sample size, varying treatment histories, and inclusion of non-fasting blood assessments. Case reports of new-onset diabetes in antipsychotic-treated youths and the known link between weight gain and metabolic abnormalities suggest that youths are at least as liable to develop metabolic abnormalities as adults. However, in pediatric RCTs, so far, only olanzapine has been associated with significant increases in glucose, insulin, and lipids (Correll ▸1,▸2). Nevertheless, the lack of significant metabolic abnormalities in the other short-term RCTs despite mostly significant weight gain needs to be interpreted with caution, as the negative findings could be due to the short-term trial duration, lack of strict fasting assessments, and to order effects in patients with more extensive past antipsychotic exposure. A recent cohort study in 272 antipsychotic-naive youth (30.1% with schizophrenia spectrum disorders) confirmed that during the first 12 weeks of treatment, olanzapine has the greatest adverse effect on body composition, which was associated with significant worsening of fasting glucose, insulin, insulin resistance and all lipid parameters, except for HDL-cholesterol (Correll et al. ▸5). By contrast, despite similar adverse effects on body composition, the metabolic effects differed across quetiapine, risperidone and aripiprazole. At least during the first 3 months of treatment, quetiapine was associated with a significant increase in most lipid parameters, whereas with risperidone lead only to a significant increase in triglycerides, and changes with aripiprazole remained non-significant. This suggests that in addition to indirect, weight-related metabolic changes, direct, weight-independent effects on glucose and lipid metabolism exist, at least for some antipsychotics.

Prolactin-related Side Effects

FGAs and SGAs can elevate prolactin levels, and these elevations appear to be accentuated in children and adolescents. Similar to adults, albeit at higher levels during adolescence, the relative potency of antipsychotic drugs in increasing prolactin is, roughly: ▸paliperidone≥ risperidone>haloperidol>

olanzapine≥ziprasidone>quetiapine≥clozapine>aripiprazole. To date, adequate long-term data are lacking to determine if hyerprolactinemia at levels found during antipsychotic therapy alters bone density, sexual maturation, or the risk for benign prolactinomas (Correll ▸1). Since aripiprazole is a partial D2 dopamine agonist, prolactin levels can decrease below baseline. To date, no adverse effects of low prolactin have been described in youth. Complicating the interpretation of the relevance of prolactin elevations in youth is the fact that sexual and reproductive system side effects related to prolactin levels are rarely directly inquired about, and youth might either not express these symptoms due to sexual immaturity or because they do not know what their normal levels of functioning ought to be.

Summary and Conclusion

Although still understudied, schizophrenia with onset in childhood and, especially, with onset in adolescence seems to be biologically and phenomenologically continuous with adulthood-onset schizophrenia, albeit being more often associated with poorer illness course and outcomes. Moreover, children and adolescents appear to be more sensitive to antipsychotic adverse effects than adults, at least compared to more chronically ill samples. As in adults, antipsychotics are more effective than placebo, with meaningful clinical effects. Moreover, also like in adults, differences in efficacy between antipsychotics seem to be much smaller and less predictable than differences in side effects and, thus, in effectiveness, which takes the short- and long-term side effect burden and treatment discontinuation rates into account. Based on this risk-benefit evaluation, it appears that second-generation antipsychotics might be preferable to first-generation antipsychotics to reduce the risk for EPS, TD, secondary negative symptoms, early treatment discontinuations and, possibly, relapse rates. However, since a number of second-generation antipsychotics are associated with significantly greater risks for age-inappropriate weight gain and metabolic abnormalities than mid and high potency first-generation antipsychotics, the neuromotor side effect advantages and related benefits are likely offset by the risk of longer-term health problems for those higher metabolic risk second-generation antipsychotics. Therefore, it appears that second-generation antipsychotics with the least risk for developmentally inappropriate weight gain and related or, even, direct metabolic abnormalities are to be considered first-line treatment options. In case these fail, higher cardiometabolic risk antipsychotics should be tried. Given the significant efficacy advantage of clozapine over first- and second-generation antipsychotics in pediatric onset schizophrenia similar to adulthood schizophrenia, clozapine should be considered for severely ill and treatment resistant youth with

schizophrenia to improve outcomes and functioning, balancing its problematic side effect profile against its superior efficacy.

Cross-References

▸First-Generation Antipsychotics
▸Schizophrenia Prodrome
▸Second-Generation Antipsychotics

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Pericyazine

Synonyms
Periciazine

Definition
Pericyazine is a first-generation antipsychotic medication that acts as a dopamine D2 antagonist. Pericyazine is indicated for the treatment of schizophrenia and other psychoses, and for short-term adjunctive treatment of severe anxiety, psychomotor agitation, excited or violent states. It is a piperazine-phenothiazine derivative and like other similar agents, it produces drowsiness and sedation. hypotension is common when treatment is initiated.

Cross-References
▸First-Generation Antipsychotics
▸Schizophrenia

Perphenazine

Definition
Perphenazine is a first-generation antipsychotic medication that acts as a dopamine D2 receptor antagonist. It is a piperazine-phenothiazine derivative, also available as depot medication. Perphenazine is indicated for the treatment of schizophrenia and other psychoses, mania in bipolar disorder, and the short-term adjunctive treatment of severe anxiety, psychomotor agitation, excited or violent states. It can also be used as an anti-emetic drug. Extrapyramidal motor symptoms occur, especially dystonia especially at high doses.

Cross-References

▸Extrapyramidal Motor Side Effects
▸First-Generation Antipsychotics
▸Schizophrenia

Pharmacogenetics of Antipsychotic Drug Response in Schizophrenia

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Definition

Pharmacogenetics is the branch of genetics investigating genes that are thought to be determinants of inter-individual variability in drug response and side effects. Pharmacogenomics is the study of the entire genome as opposed to individual genes.

Introduction

Pharmacotherapy with antipsychotics is an essential component in treatment of schizophrenia. However, more efforts need to be made to develop more effective and better tolerated antipsychotic drugs. Long-term treatment is necessary in most cases, requiring a careful selection of specific antipsychotic drug treatment for each individual in order to achieve a maximum of benefits (i.e. symptom reduction) and minimal occurrence of side effects.

Treatment plans, however, are hampered by considerable medication-related differences in the potential to alleviate symptoms such as for example the more favourable effect of second generation antipsychotics for negative symptoms on the one hand and the higher risk for metabolic adverse effects with these antipsychotics on the other. Additionally, there is a large inter-individual variance in response to specific antipsychotic drugs and in side effects. The possibility to predict individual drug response and emerging adverse effects could help to reduce apprehension in patients and clinicians caused by frequent switches of medication and reduce long-term morbidity

caused by ineffectiveness and adverse effects. This would also have beneficial effects on treatment compliance, which has been shown to be a crucial factor in long-term treatment of schizophrenia patients. Also, the risk of treatment resistance, estimated to occur in 20-40 of schizophrenic patients, could probably be lowered if an individually tailored pharmacotherapy would be available prior to treatment.

Different factors contribute to inter-individual variability in drug response. Environmental influences including diet, smoking habits or concomitant treatment as well as clinical factors such as early treatment response, duration of untreated psychosis or a history of obstetric complications, in addition to demographic factors including gender, family history and ethnicity have been shown to be of importance. As several studies have shown similar treatment response in monozygotic twins and similarities in side effects such as weight gain or tardive dyskinesia in twins or first degree relatives, a strong influence of genetic factors is likely, leading to increasing interest in pharmacogenetics studies.

In this regard, numerous genetic studies have been conducted during the past years, mostly using the candidate gene approach, i.e. the association of variants in genes thought to be involved in the pharmacokinetic or pharmacodynamic profile of a medication and variation in treatment response or occurrence of side effects. Those genetic variants include single nucleotide polymorphisms (SNPs) characterized by changes of a single base pair in the DNA sequence or changes in larger DNA segments creating insertions, deletions or multiple copies. Large numbers of SNP studies have been conducted over the past years in specific gene regions typically including regulatory regions, (e.g. the promoter) as well as protein-coding and non-coding portions of a gene. However, results have often been inconsistent, most likely caused by differences in study design and lack of control for environmental factors, which still prevents widespread use of pharmacogenetic findings in standard prescription practice (MacKenzie et al, ▸4; de Leon ▸2). Additionally, the fact that treatment response to antipsychotic drugs is not uniformly defined, and is difficult to measure, hampers conduction of studies and independent replication of positive findings. Most studies use clinician-rated scales, for example the "Positive and Negative Syndrome Scale" (PANSS), the "Brief Psychiatric Rating Scale" (BPRS) or the "Global Clinical Impression Scale" (CGI). Time periods and criteria used for definition of response differ a great deal across studies, making results less comparable.

Nonetheless, despite these challenges, some studies have delivered promising and replicable results in different genes regarding associations with treatment response and in particular with specific side effects. Now the first

attempts are being made to transfer those results into clinical practice. This chapter will review the most interesting findings with emphasis on treatment response, as pharmacogenetic studies of side effects are summarized in a different chapter. Finally, we have also included a section on the genetics of drug metabolism with emphasis on CYP450 genes.

Pharmacogenetics of treatment response

Pharmacodynamic factors

The blockade and occupancy of dopamine receptors is regarded as the main mechanism of action of antipsychotic drugs. While first generation substances exert mostly anti-dopaminergic action, most second generation antipsychotics also bind to serotonin receptors. Affinity to other neurotransmitter systems, such as those involving histamine, muscarine and noradrenaline receptors, is also likely involved in efficacy as well as in occurrence of side effects. Variations in genes encoding these molecular targets of antipsychotic drugs in the central nervous systems (CNS) influence expression, sensitivity and activity of their gene product, making them especially interesting for pharmacogenetic investigation.

Dopamine System

All first and second generation antipsychotics have a high affinity to dopamine D2 and D3 receptors (DRD 2 or 3) with some specific substances – such as clozapine -- also blocking D1 and D4. Genetic variation of dopamine receptors could therefore be regarded as crucial factors in treatment response. Thus, a large number of association studies have examined polymorphisms in genes of the dopaminergic system, mainly DRD2, which is the only receptor all current antipsychotics have as a target and thus it is assumed to play a major role in treatment response. There is convincing evidence for an association of the -141C Insertion/Deletion (Ins/Del) polymorphism in the promoter region of DRD2 with response to antipsychotic treatment. A recent meta-analysis demonstrated carriers of the deletion show a poorer drug response compared to homozygous carriers of the insertion. As for the Taq1A polymorphism, located downstream the DRD2 gene, this has been shown to be associated with treatment response in some previous studies, however, no significant differences between A1 and A2 allele carriers could be found in another study (Zhang et al., ▸10). For other DRD2-polymorphisms, such as A-241G and Ser311Cys, studies have also yielded significant findings, as well as for some haplotypes, indicating a major role of the gene in antipsychotic treatment response.

As for the DRD3 gene, a significant association between the Ser9Gly polymorphism and clozapine response has been described; although a meta-

analysis could only detect a non-significant trend (Hwang et al., ▸3). Other polymorphisms of this gene have not yet been investigated extensively, however, involvement of genetic variations in DRD3 still remains an interesting possibility.

Regarding the DRD1, DRD4 and DRD5 genes, some association findings have been published, but mixed results do not allow conclusions regarding their clinical impact to date (reviewed in Mackenzie et al. ▸4).

Serotonergic transmitter system

The serotonergic (5-HT) system has been investigated intensively in earlier pharmacogenetic studies, and 5-HT antagonism has been shown to be an important mechanism of action of atypical antipsychotics. Significant associations were reported for several SNPs in genes encoding different serotonin receptor subtypes (HTR1A, HTR2A, HTR2C, HTR3) and the serotonin transporter (5-HTT). Associations were reported mainly in regard to improvement of negative symptoms (reviewed in Nnadi and Malhotra ▸7). Overall, findings to date can be interpreted as preliminary since several positive findings could not be replicated independently.

In the HTR1A gene, encoding the $5HT_{1A}$, an association of the G-allele in the -1019C/G polymorphism with poorer improvement of negative symptoms under antipsychotic medication has been described more than once. Robust findings exist for HTR2A, in which a meta-analysis showed an association between the T-allele of 102T/C polymorphism with better response and association of the Tyr-allele of His452Tyr polymorphism with poorer clozapine response (meta-analysis in Arranz et al. ▸1). In HTR2C, the C/C-genotype of -759C/T polymorphism in the promoter region of the gene was associated with better treatment response regarding negative symptoms of drug-naive schizophrenia patients. The $5HT_3$ is the only ligand-gated ion channel among the serotonin receptors and is blocked by many antipsychotic drugs, e.g. clozapine. The role of the receptor in antipsychotic treatment response is still not clear, but some studies indicate an influence of polymorphisms in the genes for the subtypes 3A, 3B and 3E.

The serotonin transporter is an integral membrane protein transporting serotonin back from the synaptic gap into the presynaptic neuron and by doing so terminating the action of serotonin. Polymorphisms in the encoding gene of the 5-HTT protein have been associated with treatment response; most robust findings exist for the 44 bp insertion/deletion polymorphism, 5-HTTLPR, in the promoter region of the gene with the short allele being more frequent in patients with poor drug response.

Other Gene Systems

In addition to the most frequently examined genes in the serotonergic and dopaminergic systems, several studies on other genes potentially involved in treatment response have been performed with promising findings. However, further analyses are required to assess their role in more detail. In the following section, the most interesting and most recent findings are highlighted and briefly discussed.

As monoaminergic receptors are G-protein linked, differences in G-protein activity can cause changes in intracellular signal transduction. The -825C/T polymorphism in the gene encoding the β-subunit of the protein GNB3 has been shown to be associated with antipsychotic treatment response, with homozygosity for the T-allele leading to poorer response to clozapine.

In part based on its role in neurodevelopment of dopamine and serotonin circuits, some findings indicate that brain derived neurotrophic factor (BDNF) is involved in pathogenesis of schizophrenia and antipsychotic action. The Val66Met and $(GT)_n$ polymorphisms of BDNF have shown moderate association to treatment response. In schizophrenic patients responding to clozapine, the Val/Val genotype of Val66Met polymorphism was over-represented compared to the control group. Regarding the $(GT)_n$ polymorphism, the 230-bp allele was more frequent in responders to risperidone than in non-responders.

The glial-cell-line derived neurotrophic factor (GDNF) is an important neurotrophic factor for dopaminergic neurons. The genes encoding the four known GDNF-family receptors in the alpha group (GFRA) were located in chromosomal regions suggested to be linked to schizophrenia. A recent study examined SNPs in GFRA 1-4 and found an association of SNPs in GFRA 1 and 3 with schizophrenia and of a haplotype in GFRA 2 (T-G-G rs1128397-rs13250096-rs4567028) with better clozapine response.

Catechol-O-methyltransferase (COMT) is involved in the degradation of dopamine and other catecholamines and may also be a susceptibility gene for schizophrenia. The Val(158)Met polymorphism creates differences in functional activity and the Met allele has been shown to be associated with better improvement of negative symptoms and of working memory performance under antipsychotic treatment. The effect on working memory makes sense given that COMT is mostly expressed in frontal brain areas. Other polymorphisms in the gene have been moderately associated with treatment response as well, indicating an influence of a wider set of variants across COMT.

Given that a dysregulation of the immune system may be involved in pathogenesis of schizophrenia, inflammatory genes have been examined for influence on treatment response as well. In the tumor necrosis factor alpha-

(TNFα-) gene, the G-308A polymorphism has shown an association to clozapine response with a better improvement of symptoms in carriers of the A-allele.

Genome-wide association studies offer a large potential to uncover further genetic factors involved in regulation of antipsychotic treatment response. Therefore, there is an increasing interest in such studies, and first results have already been published, in particular in large study samples such as the CATIE clinical trial. In this sample, an intergenic SNP on chromosome 4p15 and SNPs in Ankyrin Repeat and Sterile Alpha Motif Domain-Containing Protein 1B (ANKS1B) and in the Contactin-Associated Protein-Like 5 (CNTNAP5) gene showed the most interesting statistical results for an association with treatment response.

In a recent genome-wide study performed in a large Japanese sample, 14 genes were identified as potentially relevant for response to risperidone, thus providing intriguing hints for further studies to elucidate the effect of these genes on antipsychotic treatment response.

In summary, several promising candidate genes involved in pharmacodynamic action of antipsychotics have been investigated during the past decades. Most robust findings exist for polymorphisms in the serotonin and dopamine systems (Souza et al. ▸9; MacKenzie et al., ▸4).

Pharmacokinetic factors

Cytochrome enzymes (CYP), especially members of CYP450 family including CYP2D6, CYP1A2, CYP3A4 and CYP2C19, play an important role in metabolism of most antipsychotic, antidepressant and anxiolytic drugs. Enzyme activity can contribute to variances in treatment response by causing differences in plasma levels, with low activity likely leading to higher drug concentrations with increased risk of side effects (and high activity likely leading to low plasma concentrations and thereby reduced efficacy of a drug. Activity of CYP enzymes is influenced by environmental factors, e.g. CYP1A2 induction by caffeine and by cigarette smoking, as well as by genetic variability, and CYP genes are highly polymorphic. In CYP2D6, more than 130 variations (SNPs) and several copy number variations (CNV) are known, leading to four main phenotypes: 1) low enzyme activity (poor metabolizers, PM) when both alleles of the gene are very low or nonfunctional, 2) intermediate enzyme activity (intermediate metabolizers, IM) with one nonfunctional allele or both alleles being partially defective; 3) normal enzyme activity (extensive metabolizers, EM) with both alleles being functional; and 4) phenotypes with increased activity (ultra-rapid metabolizers, UM) caused by possession of more than two functional alleles. As most antipsychotics including clozapine, haloperidol, perphenazine, quetiapine, risperidone or thioridazine are metabolized by CYP2D6, genotyping and

determining metabolizer status before starting treatment could be an effective and straightforward tool to help predict dosing required for a sufficient plasma level, to provide the best chance for clinical improvement, and to diminish risk of side effects. For example, the CYP2D6*3 or 4 genotype has been shown to be associated with a larger amount of induced weight gain compared to the wild-type *1/ *1 genotype. Overall, it appears that genetic screening for poor and rapid metabolizers of CYP2D6 is useful information when prescribing some specific antipsychotics and antidepressants to optimize dosing strategies in particular individuals.

CYP1A2, CYP3A4 and CYP2C19 are involved in clozapine metabolism and they are interesting candidate genes especially regarding treatment resistance. A variant in CYP1A2, CYP1A2*F, has been shown to be associated with higher inducibility in smokers, resulting in faster degradation of clozapine. Polymorphisms in CYP3A4 including the *4,*5 and *6 alleles, appear to be associated with decreased activity of the enzyme. In CYP2C19, *2 and *3 were found to be associated with the poor metabolizer (PM) phenotype, whereas CYP2C19*17 leads to increased activity due to increased transcription. As these genes have not been investigated extensively to date, our group is focusing on drug metabolism and performing further studies to determine clinical implications of CYP genotypes (for further information, see http://www.pharmacogenetics.ca).

The first attempts have been made to transfer results from investigation on drug metabolism into clinical practice. For example, the AmpliChip®CYP450 test (Roche Diagnostics, Switzerland) is an initial effort to introduce pharmacogenetic findings into drug monitoring by testing allelic variants of CYP2D6 and CYP2C19 allowing a prediction regarding metabolizer status. Although sufficient data from cost-effectiveness studies of CYP genotyping in antipsychotic treatment are still lacking and those tests have not yet been established in clinical routine, it remains conceivable that they will be part of treatment decision making in the near future. Furthermore, as more clinical genetic data is collected, the quality of CYP450 gene testing and its clinical application should improve.

Blood-brain-barrier

The P-glycoprotein (PGP) belongs to the family of adenosine triphosphate-binding cassette (ABC) transporters and functions as an efflux transporter, removing cytotoxic substances from different organs. PGPs are located in cells of the blood-brain-barrier where they remove neurotoxins and drugs from the brain into the bloodstream. An altered activity of PGP might therefore contribute to a reduced or elevated drug response, making the gene encoding PGP, the multiple drug resistance gene 1 (MDR1 or ABCB1), an interesting candidate gene for pharmacogenetic studies. Overall, studies

have been inconsistent for the MDR1 gene and antipsychotic drug response. Nonetheless, promising results have been reported for the G2677T and C3435T-polymorphisms which were found to be associated with antipsychotic response.

A summary of the polymorphisms shown to be associated with antipsychotic drug response repeatedly in different studies is given in table 1.

Table 1 Summary of most important polymorphisms associated with drug response.

Gene	Polymorphism	Main findings
DRD2	141C Ins/Del	Better response of carriers of the insertion
DRD3	Ser9Gly	Better response of homozygous carriers of the Gly-allele
HTR1A	-1019C/G	Better response of carriers of the C-allele
HTR2A	102T/C	Better response of carriers of the T-allele
HTR2C	-759C/T	Better response associated with C/C-genotype
GNB3	-825C/T	Better response of carriers of the T-allele
ABCB1	2677G/T	T-allele associated with better response
COMT	Val(108/158)Met	Better improvement of negative symptoms and working memory associated with the met-allele

Pharmacogenetics of side effects

Pharmacogenetics of antipsychotic-induced side effects are discussed in another chapter. However, since potential occurrence of side effects are equally important in treatment decisions, and because side effects are also highly associated with genetic factors, we mention the most important findings briefly below.

Antipsychotic-induced weight gain

Antipsychotic-induced weight gain is associated with social stigmata, noncompliance and higher morbidity and mortality caused by obesity, diabetes or cardiovascular disorders. Second-generation antipsychotics, most notably olanzapine or clozapine, have been shown to cause an extensive amount of body weight gain, but the large inter-individual variability indicates involvement of genetic factors, leading to substantial efforts to develop facilities to predict an individual's risk of excessive weight gain. Over the past years, a number of candidate gene studies have been conducted delivering most frequently replicated results for an association of polymorphisms in HTR2C (-759C/T), encoding 5-HT_{2C} receptors, in the Leptin gene

(-2548A/G), in SNAP-25 (*synaptosome-associated protein of 25 kDa*,, various downstream markers) and in GNB3 (-825C/T), encoding the β-3-subunit of G-protein receptors (reviewed in Müller and Kennedy ▸6). Nonetheless, inconsistent findings and small effect sizes of single polymorphisms still do not provide predictive power for the use of pharmacogenetic results in clinical practice to date.

Tardive dyskinesia

Tardive dyskinesia (TD) occurs in approximately 25 of long-term treated patients, especially after treatment with first generation antipsychotics. TD is potentially irreversible and creates considerable stigmatization for its sufferers. Given that data indicate a familial occurrence, several candidate genes have been studied for an association with TD. Most promising results were found in DRD2, DRD3 and DRD4. Also a haplotype association in NOS3, encoding endothelial nitric oxide synthase, was reported, as well as associations in CYP2D6, CYP1A2 and MnSOD, the gene encoding manganese superoxide dismutase, an antioxidant enzyme (reviewed in Müller et al. ▸5). In a recent genome-wide association study in the CATIE sample, association was described of two intergenic SNPs and one SNP in ZFN202, a transcriptional repressor controlling PLP1, a major protein in myelin, with extrapyramidal side effects. Nonetheless, more detailed investigation remains necessary to fully assess genetic influence on occurrence of TD in patients treated with antipsychotics. Also, it remains unclear if the genes with positive results might be combined into an algorithm for prediction of risk for TD.

Agranulocytosis

Only a very few studies have been performed examining genetics of clozapine-induced agranulocytosis (CIA), a potentially life threatening side effect occurring in approximately 1 of patients receiving clozapine. Significant genetic associations were found for some antigens and haplotypes in genes involved in the human leukocyte antigen system (e.g. HLA-Cw 7, HLA-Cw-B and HLA-DRB5-DRB4) as well as for microsatellite markers in the pro-inflammatory TNFα-gene (e.g. TNFd3, b4, b5), but lack of replication and the assumption of multiple, interacting genetic variations leading to such drug reactions (reviewed in Opgen-Rhein and Dettling ▸8) make further investigation necessary. Nonetheless, a commercial test (PgxPredict:CLOZAPINE®, Clinical Data Inc., USA) has become available to evaluate subjects at higher risk for CIA by testing the 6672G/C polymorphism in HLA-DQB1 with a sensitivity of 21.5 and a specificity of 98.4 for detection of high-risk patients (carriers of the C allele).

Perspectives for pharmacogenetics in antipsychotic treatment

In summary, many gene variants influencing treatment response and occurrence of side effects during antipsychotic treatment have been suggested in genetic association studies during the past years with most promising results in dopamine and serotonin receptor genes and in the cytochrome system. Ambiguous findings, in part caused by differences in study designs, small sample sizes, small effect sizes of single polymorphisms, the high complexity of genetic processes and little knowledge about gene-gene and gene-environment interaction, still limit the use of pharmacogenetic findings in clinical care. Nonetheless, the first tests using genetic information regarding drug metabolizing status of an individual before beginning antipsychotic medication, or a test detecting risk factors for agranulocytosis in the HLA-system, have been developed to begin to integrate research findings into everyday practice.

With each passing year of further investigation, and with the rapid development of DNA analysis technology, genetic information will become an inexpensive and routine tool in clinical care. Thus far, genetic investigations have limitations in the informative value of association findings for prediction of medication effects. Genome-wide association studies have delivered their first interesting results as shown above and are continuing to allow an analysis of the whole genome to identify novel genetic factors without needing a previous hypothesis. Additional strategies include investigating variations in gene transcription, RNA function, and protein modification, and examination of epigenetic variability (DNA-methylation and histone acetylation). The latter is a link between genetic and environmental factors as those DNA-modifications can be altered by stress or other factors such as smoking for example. A stronger consideration of environmental, demographic and clinical conditions in future genetic studies is desirable and could be helpful to generate more replicable results. It is hoped that the aim of an individually tailored antipsychotic treatment regime will be obtained in the near future to allow more informed treatment selection and response prediction leading to improved outcomes for patients.

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Pharmacogenetics of Drug Side Effects and Safety

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Background

For nearly 60 years, antipsychotic medications have been available for the treatment of schizophrenia and related disorders (Kapur et al., ▸1). The initial success of these agents, beginning with chlorpromazine, permitted the re-entry into society of large numbers of institutionalized patients, and they continue to form the foundation of treatment of psychosis (Terkelsen et al., ▸2). Moreover, the class of antipsychotic drugs is increasingly used across a broad spectrum of psychotic and non-psychotic presentations, including bipolar disorder (Tohen et al., ▸3), treatment-resistant depression (Philip et al., ▸4), and childhood-onset disorders such as autism and other behavioral disturbances (Olfson et al., ▸5). In the United States, for example, total prescriptions for antipsychotics (as well as the total number of patients taking antipsychotics) nearly doubled in the 10 years between 1997 and 2007, representing about 4 million individuals across a range of ages from children to the elderly (Stagnitti, ▸6).

Concomitant with the increasing rate of antipsychotic drug prescription, medication-induced side effects are a burgeoning public health problem. Typical or first-generation antipsychotics (FGAs) often cause prolactin elevations and extrapyramidal motor side effects (EPS) that are highly aversive to patients, and the risk of irreversible tardive dyskinesia (TD), estimated at ~5 per year (Kane et al., ▸7), has caused this class of agents to fall out of favor, especially in the United States. Newer, atypical or second-generation antipsychotics (SGAs) are less frequently accompanied by EPS and TD, but weight gain, metabolic changes and associated cardiovascular consequences have emerged as a major concern (De Hert et al., ▸8). These adverse medication effects, which are themselves difficult to treat or manage, significantly contribute to mortality in patients with schizophrenia, whose life expectancy may be reduced by more 20 years compared to the general population (Tiihonen et al., ▸9). While FGAs are historically associated with movement abnormalities, and SGAs with metabolic disturbance, it is important to note that these relationships are not exclusive. Studies in antipsychotic-naïve individuals demonstrate conclusively that FGAs can cause clinically significant (>7 of baseline) weight gain in about half of all patients (Kahn et al., ▸10), while rates of TD due to SGAs may exceed 10 (Correll et al., ▸11).

Unfortunately, there is little clinical research that can effectively guide psychiatrists in the selection of antipsychotic agent for a particular patient. Most antipsychotics fail to differentiate from each other in terms of efficacy (Leucht et al., ▸12), and real-world trials are marked by only partial efficacy, poor adherence, and high rates of discontinuation (Leucht et al., ▸12, (Lieberman et al., ▸13)). The two medications with evidence for superior

reduction of clinical symptoms, olanzapine and especially clozapine (Leucht et al., ▸12, Lieberman et al., ▸13, Kane et al., ▸14), tend to produce the most extreme metabolic disturbances (Rummel-Kluge et al., ▸15), and clozapine carries additional liabilities for treatment-emergent agranulocytosis, which can be fatal (Alvir et al., ▸16). In large-scale effectiveness trials, clinically significant side effects are noted in the majority of patients on any antipsychotics, and tolerability is the primary cause of at least 20 of all drug discontinuations (Lieberman et al., ▸13). At the same time, there is marked inter-individual variability in the tendency of patients to manifest any given side effect from a particular medication.

Consequently, reliable prediction of liability to particular forms of antipsychotic-induced adverse events would represent an important advance in the clinical management of severe mental illness. A few demographic and clinical predictors of side-effect susceptibility have emerged: 1) Age manifests an inverted-U relationship with liability, such that the oldest and youngest patients are most susceptible to APD-induced adverse events (Jeste et al., ▸17, Correll, ▸18); 2) Patients experiencing extrapyramidal symptoms have twice the risk for TD as patients without EPS (Tenback et al., ▸19); 3) APD dose is only very weakly correlated with these effects, and even low doses may carry substantial risk (Casey, ▸20).

Beyond these broad generalizations, molecular genetic approaches (broadly termed "pharmacogenetics" or "pharmacogenomics") have arguably provided the most promising avenue for dissecting the heterogeneity of antipsychotic adverse events; as detailed below, several common genetic variants have been replicably associated with antipsychotic-induced side effects including movement abnormalities and weight gain. Moreover, pharmacogenomics provides a number of distinct advantages in the search for predictors of adverse events (Malhotra et al., ▸21). First, an individual's genotype does not change as a result of treatment or illness state, and thus, the assay can be obtained at any time during the course of illness and treatment. Second, current molecular technologies provide a highly accurate assessment of an individual's genotype, with virtually negligible measurement error. Third, publicly available databases (International HapMap 3 Consortium, ▸22) now provide the necessary data to conduct comprehensive, unbiased studies of the entire genome. Finally, costs of genotyping are dropping at an exponential rate, with the real possibility of an affordable whole-genome sequence for each patient on the horizon.

Pharmacogenetic Studies of Antipsychotic-Induced Side Effects

Tardive Dyskinesia. Tardive dyskinesia (TD) encompasses a range of chronic, involuntary body movements, which can be physically debilitating,

socially stigmatizing, and irreversible. The etiology of TD has never been fully explicated, but it is thought that the dopamine antagonism common to all antipsychotic drugs (Kapur et al., ▸23) results in up-regulation of D2 receptors and subsequent hyperactivity in the nigrostriatal dopaminergic tract, which is closely involved in the regulation of motor behavior. Tardive dyskinesia is the most extensively studied APD-induced side effect in the pharmacogenetics literature to date, with the greatest focus on the role of dopamine-related genes. These studies have typically been cross-sectional in nature, with ascertainment based on retrospective identification of cases with varying treatment histories and duration. While permitting the examination of large sample sizes, this ascertainment strategy may suffer from false negatives (patients with mild or reversible TD) and false positives (patients with acute motoric abnormalities that do not persist, and patients with pre-existing movement abnormalities).

Most pharmacogenetic studies of TD have examined variation related to the *DRD2* gene, which codes for the protein that constitutes the dopamine D2 receptor. The largest number of studies has examined the so-called Taq1A polymorphism (rs1800497), which more recently has been determined to lie outside of *DRD2* itself, and is instead a nonsynonymous coding SNP in a neighboring ankyrin repeat gene (*ANKK1* Glu713Lys) (Neville et al., ▸24). Possibly due to linkage disequilibrium with another site (or sites) within *DRD2*, the minor (T) allele (also called the A1 allele) at rs1800497 has been associated with a 40 reduction in striatal D2 receptor density based on both *in vitro* assays and *in vivo* imaging studies (Thompson et al., ▸25, Pohjalainen et al., ▸26). Consistent with the dopaminergic up-regulation hypothesis, this allele appears to be protective against TD. Despite the fact that only 2 out of 8 individual studies to date reported significant findings, a cumulative sample of 1,256 patients (507 with TD and 749 without TD) from 6 cohorts demonstrated an odds ratio of 1.30 for the risk of TD in the A2 allele (Zai et al., ▸27). This means that each copy of the A2 allele confers a 30 more risk of developing TD, relative to the A1 allele. Compared to A1/A1 homozygotes or A1/A2 heterozygotes, patients with the A2/A2 genotype have a 50 increased risk of TD (odds ratio = 1.50). Other SNPs in DRD2, including -141C Ins/Del and Ser311Cys, have not been found to affect TD development, despite their promising roles in predicting clinical response to antipsychotic treatment (Bakker et al., ▸28).

Like the D2 receptor, the dopamine D3 receptor is also selectively expressed in the basal ganglia and is considered to be a target of antipsychotic action; consequently, several pharmacogenetic studies in schizophrenia have examined the *DRD3* gene. D3 may be an especially promising correlate of drug-induced movement disorders, insofar as blockade of the D3 receptor in the

basal ganglia produces hyperactivity in animal models (Accili et al., ▸29). Moreover, antipsychotic drugs that have minimal D3 affinity, such as clozapine and quetiapine, tend to have lower liability of causing TD (Miller et al., ▸30). One missense SNP in DRD3, Ser9Gly, has been associated with clinical response to antipsychotic drugs; specifically, carriers of the Gly allele demonstrate enhanced symptom reduction in antipsychotic trials (Szekeres et al., ▸31, autor et al. ▸32). Correspondingly, the Gly allele has been associated with higher risk of TD in at least 8 studies, and this was confirmed in two early meta-analyses with overlapping samples (Bakker et al., ▸33, Tsai et al., ▸34). However, the effect size for TD risk is modest (OR=1.16 in the largest meta-analysis), with diminishing effects in the most recent studies. This pattern of diminishing effect size estimates over time, termed "the winner's curse", is common in genetics studies and can ultimately result in rejection of the initial finding as a false positive (Xiao et al., ▸35). Moreover, a very recent study in the large CATIE cohort (n=207 cases with TD vs 503 cases without TD), which was not included in any meta-analysis, demonstrated essentially no effects of either *DRD3* Ser9Gly or *DRD2* Taq1A (Tsai et al., ▸36). However, it should be noted that even this relatively large study was underpowered to find effect sizes of 1.5 or smaller.

A third dopamine-related gene that has been investigated in multiple pharmacogenetic studies of TD is Catechol O-methyltransferase (*COMT*). COMT is the predominant mechanism of dopamine clearance in frontal cortex, and this gene contains a well-studied functional polymorphism that codes for a substitution of methionine (met) for valine (val) at codon 158 (Männistö et al., ▸37). The met allele, which is fairly common (35-48) across all human populations, results in a thermolabile protein that has one-fourth the enzymatic activity of the val-carrying form (Lachman et al., ▸38). (In other words, the val allele results in reduced synaptic dopamine due to more rapid clearance). Across five studies included in a recent meta-analysis (Kapur et al., ▸39), the val allele was associated with modestly increased risk for TD (OR=1.19). It is unknown whether this counter-intuitive protective effect of the met allele is a direct result of subcortical COMT activity, or is secondary to alterations (e.g., upregulation) in fronto-striatal circuitry.

In addition to dopamine antagonism, the second generation antipsychotics almost uniformly feature near-saturation binding of serotonin 5-HT_2 receptors (Kapur et al., ▸39). Since SGAs produce lower incidence of TD, it is a reasonable hypothesis that risk for TD may be modulated by variation in serotonin-receptor genes. For example, a promoter region SNP (rs6313) in the 5-HT_{2A} receptor gene (*HTR2A*) has been examined in several pharmacogenetic studies of TD; this SNP has been previously associated with response to antipsychotics (Arranz et al., ▸40) as well as antidepressants

(Kato et al., ▸41). Paradoxically, the C allele which is associated with reduced clinical efficacy in terms of symptom response (Arranz et al., ▸40), has been associated with significantly *increased* risk for tardive dyskinesia (Lerer et al., ▸42). A recent meta-analysis reported an odds ratio of about 1.6 for C allele carriers across 6 studies; effects were strongest in older patients (age > 47 years), and were specifically associated with limb-truncal (but not orofacial) TD (Lerer et al., ▸42). Mechanistically, since this allele tends to be associated with reduced expression of the receptor (Myers et al., ▸43), it can therefore be inferred that reduced availability of the 5-HT_{2A} receptor is a risk factor for tardive dyskinesia. Notably, 5-HT_{2A} receptors are strongly expressed in the caudate and putamen (Waeber et al., ▸44) , and recent evidence obtained from dopamine-depleted rodents suggests a complex interplay of subcortical dopamine and serotonin in the regulation of motor behavior (Bishop et al., ▸45) .

In addition to dopamine and serotonin receptors that are major target of antipsychotic drugs, genetic variation in metabolic pathways of the drugs have also been studied in association with TD. Theoretically, if a drug is not cleared fast enough, prolonged stimulation of dopamine receptors may put patients at risk of developing TD. Many commonly prescribed antipsychotics, including both FGAs (haloperidol, perphenazine, thioridazine) and SGAs (risperidone and aripiprazole), are metabolized in the liver by CYP2D6 (debrisoquine hydroxylase) (Caccia, ▸46). The CYP2D6 gene is highly polymorphic, with some variations (null alleles) causing impaired protein function. Homozygosity for null alleles gives rise to the "poor metabolizer" phenotype characterized by no enzyme activity while null allele heterozygosity gives rise to an intermediate phenotype characterized by reduced enzyme activity resulting in a higher effective dose (Bertilsson et al., ▸47). Consistent with this pharmacokinetic prediction, a meta-analysis of 8 studies demonstrated a moderate effect of (any) loss of function alleles on risk for TD (OR=1.43), while homozygotes (poor metabolizers) had 1.64-fold greater odds of suffering tardive dyskinesia (Patsopoulos et al., ▸48). A recent small study further confirms these results (Kobylecki et al., ▸49). A similar effect has been studied for *SOD2*, the gene encoding manganese superoxide dismutase, a mitochondrial enzyme involved in oxidative metabolism. A functional SNP (Ala9Val), affecting efficiency of MnSOD transport, has been associated with TD risk; counterintuitively, the less efficient val allele is protective; homozygotes for the Ala (T) allele are about twice as likely to develop TD compared to val carriers (Bakker et al., ▸33).

Extrapyramidal symptoms. Compared to the large number of studies on tardive dyskinesia, there are few pharmacogenetic studies of EPS. However, a handful of studies have reported effects that are parallel to those reported

for TD. For example, (Eichammer et al., ▸50) reported increased incidence of akathisia amongst *DRD3* Gly carriers, although this finding has not been replicated (Gunes et al., ▸51, Guzey et al., ▸52). One additional study identified another *DRD3* SNP (rs167771) which was associated with EPS in a study of 270 risperidone-treated patients (Gassó et al., ▸53), but this result also awaits replication. One small study has demonstrated an effect on EPS risk for the C allele of rs6313 in *HTR2A* that parallels its effect on TD (Gunes et al., ▸51). Although not previously examined in TD studies, a SNP in *RGS2* (rs4606) has been associated with extrapyramidal symptoms in two studies (Greenbaum et al., ▸54, ▸55). Although a third study was negative, this regulator of intracellular dopamine signaling merits additional research (Al Hadithy et al., ▸56).

Prolactin elevation. While prolactin elevation has also not been widely studied, there have been seven studies of the Taq1A variant at *DRD2* (Calarge et al., ▸57, Kwon et al., ▸58, Yasui-Furukori et al., ▸59, Aklillu et al., ▸60, Anderson et al., ▸61, Young et al., ▸62, Mihara et al., ▸63). Three of these studies have been positive, reporting that the A1 allele was associated with increased risk for hyperprolactinemia. A fourth study demonstrated the same effect in females only. This is the opposite allele that was associated with TD, which may reflect the fact that prolactin response is mediated via the tuberoinfundibular pathway (hypothalamus and pituitary) (Compton et al., ▸64), rather than through the basal ganglia.

Clozapine-induced agranulocytosis (CIA). As noted previously, clozapine is the only antipsychotic medication with reliably enhanced efficacy for the treatment of chronic schizophrenia (Kane et al., ▸14, McEvoy et al., ▸65). However, it is underutilized in clinical practice (Rothbard et al., ▸66), due to the risk of agranulocytosis, a rare, yet potentially life-threatening, reduction in absolute neutrophil count that requires the patient to be subjected to ongoing, frequent blood monitoring (Alvir et al., ▸16). Consistent with an immunological mechanism, CIA generally recurs rapidly upon rechallenge with clozapine (Athanasiou et al., ▸67). Therefore, several investigators have examined relationships between CIA and genotype at HLA (human leukocyte antigen) markers located on chromosome 6p; these studies have converged on alleles in the class II MHC (major histocompatibility complex) (Dettling et al., ▸68, Athanasiou et al., ▸69), consistent with earlier studies using conventional HLA typing (Amar et al., ▸70). Notably, pharmacogenetic studies of rare, extreme reactions to other classes of medication have also implicated MHC (Daly et al., ▸71, Martin et al., ▸72). Although HLA-DQB1 alleles have demonstrated high positive predictive value, with odds ratios as high as 17 (Athanasiou et al., ▸69), the sensitivity of this test remains low, so that individuals without these risk alleles still have non-

neglible risk for CIA, necessitating continued blood monitoring. To date, no other genetic risk factors have been reliably demonstrated, and further studies will be needed to generate a sufficiently predictive risk profile that may reduce the need for invasive blood monitoring.

Weight gain. Because antipsychotic-induced weight gain has been particularly prominent with certain SGAs, it has been suggested that increased serotonin binding profiles may account for the increased liability to weight gain observed in the second-generation antipsychotics (Reynolds, ▸73). In preclinical models, increasing serotonin results in decreased feeding; conversely, with reduced serotonin leads to increased appetitive behavior (Adan et al., ▸74). Since pharmacologic agonists of 5-HT2C specifically lead to decreased feeding in animals (Davis et al., ▸75), it is logical to speculate that 5-HT2C antagonists, including most second generation antipsychotics, might lead to increased food intake.

The most widely-studied pharmacogenetic predictor of antipsychotic-induced weight gain is a promoter region polymorphism, -759 T/C (rs3813929), in the *HTR2C* gene (on the X chromosome). For example, Reynolds and colleagues (Reynolds et al., ▸76) studied 123 drug-naïve Chinese patients treated primarily with risperidone or chlorpromazine. Subjects carrying the T allele at this locus gained significantly less weight than subjects with no T allele, and none of the 27 subjects with the T allele met criteria for severe (>7) weight gain after 6 weeks. Two studies (Miller et al., ▸77, Reynolds et al., ▸78) in clozapine-treated patients also demonstrated a protective effect of the T allele, and Ellingrod and colleagues (Ellingrod et al., ▸79) reported similar effects for olanzapine-treated patients. (Lane et al., ▸80) extended these findings to include risperidone, and several studies have reported the reduced weight gain for T allele carriers in heterogeneously-treated cohorts (Reynolds et al., ▸81). While a few studies have failed to replicate these results, it should be noted that these studies were restricted to chronic patients with extensive prior treatment. A meta-analysis of 8 studes demonstrated that T allele carriers have less than half the rate of clinically significant (7-10 or greater) weight gain from baseline compared with the C allele at this SNP (Reynolds et al., ▸81).

Although weight gain has emerged as the most conspicuous side effect of SGAs, it is important to note that most FGAs also demonstrate a weight-gain liability. For example, a recent study in first-episode patients demonstrated clinically significant (>7) weight gain in more than half of patients treated with low-dose haloperidol, and in nearly two-thirds of patients treated with amisulpride, which has no serotonergic binding (Kahn et al., ▸10). Nevertheless, dopamine-related genetic variation only rarely been considered in pharmacogenetic studies of weight gain. A very recent study

(Lencz et al., ▸82), however, examined the relationship between this phenotype and a *DRD2* functional promoter polymorphism (-141C Ins/Del, rs1799732) which has been demonstrated to affect transcription levels of the dopamine D2 (Arinami et al., ▸83). Although the sample was relatively small (n=58), power was enhanced by the fact that more than 75 of patients were antipsychotic-naïve, and none had greater than 12 weeks of prior treatment with any antipsychotic agent; thus, the weight-gain phenotype was not confounded by effects of prior drug exposure. Additionally, these first-episode schizophrenia patients were enrolled in a 16-week randomized, prospective trial of risperidone vs. olanzapine. Regardless of drug assigned, deletion carriers at this SNP (i.e., those missing a letter "C" at this genomic location) experienced substantially greater weight gain beginning at 6 weeks of treatment. By the end of the 16 week trial, genotype accounted for nearly a fifteen pound difference in weight gain (Lencz et al., ▸82).

One gene involved in intracellular signaling has been repeatedly examined with respect to APD-induced weight gain: *GNB3* encodes a subunit of a heterotrimeric guanine nucleotide-binding protein (G protein), which integrate signals between receptors and effector proteins (Rosskopf et al., ▸84). A single-nucleotide polymorphism (C825T) in this gene has been associated with essential hypertension and obesity; this SNP is also associated with relative prevalence of a high-activity splice variant of GNB3 (Siffert et al., ▸85). According to a recent meta-analysis, five studies have examined effects of this SNP on APD-induced weight gain; the T allele was marginally associated with increased weight gain (Souza et al., ▸86). However, this effect was consistent with its effect on BMI and other metabolic variables in the general population, so the mechanism in the context of APD treatment remains unclear.

Recent genomewide association studies (GWAS) provide strong evidence for several genes including FTO, MC4R, TMEM18, and others in obesity and obesity-related phenotypes (Renström et al., ▸87), and have the advantage of drawing on extremely large sample sizes (n>10,000) from the general population. These studies provide fertile ground for developing testable hypotheses on the mechanisms of antipsychotic-induced weight gain. To date, only one GWAS has been published on weight gain and related phenotypes in the context of antipsychotic treatment (Adkins et al., ▸88). Despite the heterogeneity of treatment conditions and patient history in this sample, several promising new leads were reported, including genomewide-significant results for a polymorphism in *MEIS2* for waist- and hip-circumference in risperidone-treated patients. Intriguingly, this gene is involved in pancreatic development and function (Hui et al., ▸89). Future

GWAS in antipsychotic-naïve cohorts may have still greater power to detect relevant molecular mechanisms.

Conclusions and Future Directions

To date, pharmacogenetic studies have successfully demonstrated that a few genetic variants are replicably associated with the common antipsychotic-induced motoric and metabolic side effects. However, three factors limit the ability of the psychiatry to deliver on the promise of personalized medicine, and point to critical issues for the next generation of pharmacogenetics in schizophrenia. First, a treating psychiatrist would be unable to select a particular medication for a given patient, due to the lack of pharmacogenetic head-to-head comparisons, by genotype, of different treatments; such trials would be especially difficult due to the fundamental similarities of mechanism for both first- and second-generation antipsychotics . Second, even fairly consistent single-gene results, such as those observed for *DRD3* and TD, fail to provide large enough effect sizes to make confident clinical decisions. Third, the economics of conducting pharmacogenetic tests on a large clinical scale will need to be justified to payers, including the insurance companies and the federal government. In order to do so, pharmacogenetics researchers will need to quantify the beneficial economic impact of tailored prescription practices (Perlis et al., ▸90).

Of course, any personalized clinical decision-making process will optimally include validated predictors of symptom response as well as adverse effects. The variability in symptom response ranges from patients who experience rapid symptom remission to a subset of patients often described as "treatment refractory" (Tandon et al., ▸91). Even when fully adherent with medication, as many as 40 of patients fail to demonstrate adequate response on the hallmark positive symptoms of hallucinations and delusions (Conley et al., ▸92). Unfortunately, the literature on pharmacogenetics of response is more difficult to summarize than for side effects; due to wide differences in trial methodology and definition of dependent measures, only a single meta-analytic study has been published in the last decade (Zhang et al., ▸93). This report identified a significant effect of the afore-mentioned *DRD2* -141C deletion allele on response to antipsychotic treatment. Deletion allele carriers demonstrated reduced likelihood of experiencing a significant clinical response (40-50 reduction in symptom ratings), despite the fact that this same allele was associated with *increased* side effect liability in the weight gain study described above. Clearly, further studies are needed to understand the particular vulnerabilities of this genetic subgroup. Additionally, an early meta-analysis of clozapine response identified an effect of *HTR2C* T102C, as described earlier (Arranz et al., ▸40).

In the future, much larger prospective studies will be required to have sufficient statistical power to utilize new genomewide technologies, and to determine whether application of a pharmacogenetic risk profile is clinically and economically advantageous. From a methodological perspective, studies of first episode patients may also enhance power by minimizing potential confounds associated with chronic illness and variable history of prior treatment; first episode cohorts are also marked by reduced duration of psychotic symptoms, substance abuse, and functional/social disabilities (Lencz et al., ▸94). By contrast, studies of chronic schizophrenia may systematically over-represent patients who are not fully responsive to treatment or are nonadherent to treatment (or both), and underestimate APD response. First episode samples may be less biased on these factors and therefore may be more informative about the spectrum of outcomes with APD treatments. While large-scale prospective trials involving first episode cohorts are logistically challenging, such studies would hold substantial promise for advancing the field in the next decade.

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Phencyclidine

Synonyms

▸Angel dust
PCP

Definition

Phencyclidine (PCP) was originally developed as a general anesthetic agent by Park-Davis & Co. in the late 1950s, but during the initial clinical trials it was discovered that approximately 30% of the patients, as they emerged from anesthesia, developed psychotic reactions that had a close resemblance to ▸schizophrenia. Subsequent studies found that after intravenous administration PCP induced a dysphoric, confusional state characterized by feelings of unreality, changes in body image, profound sense of aloneness or isolation, and disorganization of thoughts and amnesia; in many subjects negativism and hostility also occurred together with ▸hallucinations and repetitive motor behavior. PCP could in healthy volunteers produce schizophrenia-like impairment of primary attention, motor function, proprioception, and symbolic and sequential thinking. Despite its dysphoric profile in patients, PCP was subject to abuse under the street name "Angel dust". Its primary mechanism of actions is noncompetitive inhibition of the ion channel of the NMDA receptor, by binding inside the channel. However, PCP is also a muscarinic antagonist, a dopamine, 5-HT and noradrenaline reuptake inhibitor, a sigma 1 and 2 ligand, a cholinesterase inhibitor, and can block voltage-gated potassium channels.

Cross-References

▸Antipsychotic Drugs
▸Ketamine
▸Phencyclidine

Phenothiazines

Definition

A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in treatment of schizophrenia. Among the widely used drugs in this category are chlorpromazine, trifluoperazine, and fluphenazine.

Cross-References

▸First-Generation Antipsychotics

Pimozide

Definition

Pimozide is a first-generation antipsychotic that acts as a dopamine D2 receptor antagonist. It is a diphenylbutylpiperidine derivative with high potency, a receptor binding profile comparable to that for ▸haloperidol but more selective for the D2 receptor, and it has a long half-life. Following reports of sudden unexplained deaths the Committee on the Safety of Medicines recommended ECG before treatment. A history of arrhythmias or congenital QT prolongation is a contraindication for its use. Pimozide should not be combined with other potentially arrhythmogenic drugs. It has been regarded as a less-sedating compound but the frequency of extrapyramidal symptoms is relatively high.

Cross-References

▸First-Generation Antipsychotics
▸Schizophrenia

Postpsychotic Depressive Disorder of Schizophrenia

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Synonyms

Associated depression in schizophrenia
Depression superimposed on residual schizophrenia

Depression NOS
Postpsychotic depression
Secondary depression in schizophrenia

Definition

Postpsychotic depressive disorder of schizophrenia (PPDDS) is a clinical condition that occurs when an individual with the pre-existing diagnosis of ▸schizophrenia manifests the syndrome of depression subsequent to the remission, or partial remission, of a florid psychotic episode of schizophrenia. PPDDS is diagnosed only during the residual phase of schizophrenia that follows the active psychotic phase (the active phase representing the presence of symptoms meeting Criterion A of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – DSM-IV) (American Psychiatric Association ▸1) (DSM-IV). Negative symptoms or attenuated manifestations of active phase symptoms (e.g., odd beliefs or unusual perceptual experiences) may, however, persist at the time of diagnosis of PPDDS. The diagnosis of PPDDS requires the presence of features sufficient to meet the DSM-IV criteria for the diagnosis of a major depressive episode and must also, specifically, include the presence of depressed mood (Emotion and Mood). Symptoms that are due to the direct physiological effects of medication, a substance of abuse, or general medical condition are not counted toward the diagnosis of PPDDS.

Context of the Definition of "Depression"

"Depression" is a term that can be used in a variety of contexts. It can refer to an affect, a symptom, a syndrome, or a disease. As an affect, the term "depression" refers to the experience of sad mood, which is an appropriate response to a stimulus such as a sad event or sad story. This is part of a full range of appropriate affect and is not pathological.

As a symptom, the term "depression" refers to a mental state involving an experience of sadness, joylessness, and/or emptiness, which is exaggerated in comparison to the circumstances and is associated with psychic pain or distress. The degree to which this type of "depression" is pathological depends on the degree of exaggeration and the amount of suffering that is involved.

The syndrome of "depression" occurs when a defined group of signs and symptoms is present simultaneously with adequate severity and duration. The DSM-IV definition of "depression" is the most common contemporary definition of "depression" and this definition is at the level of a syndrome. It includes features such as sad mood or tearfulness, sleep disturbance, appetite disturbance or fluctuations in weight, reduced energy level or excessive fatigue, psychomotor agitation or retardation, anhedonia, reduced

interest level, impaired concentration or ability to think or make decisions, feelings of excessive or inappropriate guilt and/or worthlessness, pessimism, feelings of helplessness and/or hopelessness, recurrent thoughts of death, and suicidal ideation, intent, or behavior. Interestingly, many of these features were initially incorporated into the DSM-III diagnosis of "depression" (the predecessor of DSM-IIIR and, more recently DSM-IV) on the basis of their being associated with a favorable response to an antidepressant (at that time meaning a tricyclic or MAO-inhibitor) medication. Other widely recognized features of depression at the syndrome level that were not quite as predictive of response to early antidepressant medications (e.g., diurnal variation) did not become part of the DSM-III diagnostic definition. The definition of "depression" as a disease state would require an in-depth understanding of the causation and pathophysiology of depression as a distinct biomedical condition – which is arguably still beyond our grasp. To wit, we as yet have no "tissue level" diagnostic criteria (such as a blood test, electrophysiological or imaging test, biopsy, or even autopsy finding), which confirms the diagnosis of "depression". Indeed, we cannot even be certain that the diagnosis of "depression" really belongs at the disease level, or whether "depression" is better characterized (like fever, seizures, or congestive heart failure) as being a clinical syndrome (syndrome-level diagnosis), which can occur in a variety of different "disease" states.
The definition of PPDDS given earlier is at the level of a syndrome.

Epidemiology

"Depression" has long been described as a feature in many patients diagnosed as having schizophrenia (McGlashan and Carpenter ▸5), and many studies have been undertaken to explore and/or document the frequency of occurrence of depressive symptoms and/or depressive syndromes in people with schizophrenia (Siris and Bench ▸9). These studies have varied considerably in terms of the populations that were assessed, the definitions of schizophrenia and depression, which were employed, the interval of observation which was involved, and the setting and treatment situation of the patients. The results for the observation of depression occurring in schizophrenia have ranged from a rate of 6% to 75%, but both the modal and the median frequency of occurrence was 25%. "Depression" has been associated with higher rates of adverse outcomes in schizophrenia, such as poor social adjustment, reduced quality of life, undesirable life events, relapse into psychosis, and rehospitalization. Additionally, it is of importance that the symptom or syndrome of depression, along with the symptom of hopelessness and the occurrence of events involving loss, have been identified as the most frequent correlates of suicidal ideation and behavior in schizophrenia,

a tragic outcome that has been estimated to occur at a frequency of 4–12% in schizophrenia (Siris ▸8) (Suicide).

Differential Diagnosis

There are a variety of conditions that can present with the clinical features representative of PPDDS (Siris ▸7; Siris and Bench ▸9). These include medical disorders, effects of treatments used for medical disorders, effects of other substances, neuroleptic side effects (including ▸akinesia, ▸akathisia, and neuroleptic-induced dysphoria), negative symptoms of schizophrenia, acute and chronic disappointment reactions, the prodrome of psychotic relapse, ▸schizoaffective disorder, and the expression of an independent primary diathesis for depression in an individual who also has schizophrenia.

Sad mood and/or a syndrome that can mimic depression can be a feature of a variety of medical conditions including anemias, endocrinopathies, metabolic abnormalities, infectious diseases, cancer, cardiovascular, autoimmune, or neurological disorders. Many commonly prescribed medications can also have depression occurrence as a side effect. These include beta-blockers, various other antihypertensive medications, sedative hypnotics, antineoplastic agents, nonsteroidal anti-inflammatory agents, sulfonamides, and indomethacin. Other medications can be associated with depression at the time of their discontinuation (Withdrawal Syndromes). Examples of these include corticosteroids and psychostimulants. Various substances of use and/or abuse (e.g., alcohol, cannabis, or cocaine) can also be associated with depression-like presentations, either at the time of their acute use, chronic use, or discontinuation. Additionally, the withdrawal state from two commonly used legal substances, nicotine and caffeine, can also involve dysphoria and other features that can easily be interpreted as the syndrome of depression.

Antipsychotic medications, perhaps more frequently, first-generation antipsychotics, have been associated with side effects that can also be phenocopies of depression (Awad ▸2) (▸First-Generation Antipsychotics). It may be relevant to this observation that ▸dopamine is an important neurotransmitter in the "pleasure" pathways of the brain. Thus, blocking dopamine receptors, as antipsychotic medications do, could lead to an experience that is the opposite of pleasure. This effect has been described either as a primary impact of neuroleptic agents on mood or as a component of one of the two classical extrapyramidal neuroleptic side effects of akinesia or akathisia (Medication-induced movement disorder). Akinesia is marked by a general diminution of motor behavior, causing patients to appear to be non-spontaneous, i.e., "as if their starter-motor is broken". Akathisia reflects the opposite of this: patients' appearance (frequent fidgeting and/or restless

movements) and subjective experience is "as if their starter-motor won't turn off". Both akinesia and akathisia can be associated with substantial dysphoria, and akathisia has been associated with suicide risk. Both akinesia and akathisia can also be present in subtle rather than blatant forms. Subtle akinesia can occur in the absence of large muscle stiffness or cogwheel rigidity. Subtle akathisia may be reflected in a generalized tendency toward behavioral excesses, such as over-talkativeness or wandering into other people's territory.

"Negative" symptoms of schizophrenia can also present as a phenocopy of depression. Loss of pleasure, loss of interest, and decreased activity and/or initiative are features of the negative symptoms syndrome, which have their counterparts in depression, and this is a central reason why affective features (manifest sad mood) and cognitive features (guilt, hopelessness) are so important in distinguishing depression from negative symptoms in schizophrenia. The phenotypic similarities between "negative" symptoms, "parkinsonian" symptoms, and "retarded depression" have given rise to speculation that each of these expressions may represent the common syndrome of "akinesia" being manifest in each of these situations (Bermanzohn and Siris ▸3).

In addition to the aforementioned biological and pharmacological issues, persons with schizophrenia often have much to be disappointed about in terms of how their lives are progressing in comparison to their hopes and original expectations. Consequently, both acute and chronic disappointment reactions are common. Acute disappointment reactions are generally relatively brief and can be linked to some recent event that was damaging to the patient's wishes, prospects, self-concept, or self-esteem (taking into account, of course, that such an insult is not always obvious in the face of potential idiosyncrasies of the patient's thinking or communication). Chronic disappointment reactions (also sometimes referred to as the demoralization syndrome) of longer, even open-ended, duration are based on a history of repeated failures or losses, and consequently can be more difficult to disentangle from other types of depression occurring in the course of schizophrenia (Frank ▸4).

Another important condition that can mimic depression in schizophrenia is the prodrome of psychotic relapse (Prepsychotic States and Prodromal Symptoms). When decompensating into a new psychotic episode, a patient may become dysphoric, anhedonic, restless and/or withdrawn, pessimistic, or apprehensive. Such an individual may also experience sleep or appetite disturbances, unstable energy levels and/or difficulty concentrating. The feature that distinguishes this state from depression is the eventual emergence of frank psychotic symptomatology, but this feature may not make

its appearance for a week or more. In the interim, the patient's condition may strongly mimic that of depression.

Schizoaffective disorder also enters into the differential diagnosis of PPDDS (▸Schizoaffective Disorder). To be diagnosed with schizoaffective disorder, a patient must have a period of overlap between florid psychotic symptoms and either a major depressive episode, a manic episode, or a mixed episode, as well as a period of at least 2 weeks of florid psychotic symptoms (including ▸hallucinations or delusions) in the absence of prominent mood symptoms during the same episode of illness. Additionally, for the diagnosis of schizoaffective disorder, the symptoms that meet the criteria for the mood episode must be present for a "substantial portion" of the total duration of the active and residual phases of the illness (American Psychiatric Association ▸1). Some authors also consider it to be a case of PPDDS when a patient with schizoaffective disorder (rather than the diagnosis of schizophrenia) manifests the syndrome of depression subsequent to the resolution of florid psychotic symptomatology (Siris and Bench ▸9).

Finally, there is the case where PPDDS may be manifest in a patient who has co-existing independent diatheses for the psychosis of schizophrenia and for the syndrome of depression. The argument that this, logically, would be a statistical rarity is countered by the argument that the respective diatheses may well be continuous variables rather than categorical ones – and that each diathesis may promote or aggravate the expression of the other (Siris ▸7).

Role of Pharmacotherapy

Initial Approaches

When a patient presents with a new episode of PPDDS, the first response should not necessarily be to change medications. Rather, a careful study of history needs to be done, which would include an assessment of any recent changes in medications (psychiatric or otherwise and including attention to adherence issues), a consideration of possible medical conditions, an exploration of potential psychosocial stressors, and an investigation of the possible use (or discontinuation) of substances. An exploration of risk factors for suicide is also indicated, and protective steps to safeguard the patient should be taken if necessary (Siris ▸8). The initial intervention would be to raise the level of monitoring and provide supports. If the "depression" is an acute disappointment reaction, it will resolve itself. If it is a component of the prodrome of a new psychotic episode, that also will soon declare itself, and the increased monitoring will maximize the opportunity to attenuate the episode with appropriate treatment, thereby limiting psychiatric and social/vocational morbidity. Medical conditions, the role of medications

employed to treat medical conditions, and the possible role of substance use or abuse can also be addressed in this initial phase.

Treatment of the Persisting Syndrome of PPDDS

When it is apparent that the syndrome of PPDDS is stably present, and in particular it is clear that the patient is not in the process of deteriorating into a new psychotic episode, it is appropriate to consider whether the dosage of antipsychotic medication is excessive (▸Antipsychotic Drugs). Unnecessary high doses of antipsychotic medication may contribute to neuroleptic-induced dysphoria or the neuroleptic side effects of akinesia or akathisia. Once antipsychotic medications have been established at the lowest doses, which are consistent with adequate antipsychotic activity in a given patient, the treatment of akinesia can be undertaken with adjunctive antiparkinsonian medication (▸Anti-Parkinson Drugs). For example, benztropine may be tried in doses up to a full dose of 2 mg po TID, anticholinergic side effects permitting. Occasionally, even higher doses of antiparkinsonian medications may be tried if anticholinergic side effects such as constipation, difficulty in urinating, or dry mouth (a crude but meaningful test for the bioavailability of the anticholinergic effect) are not present and the akinesia persists. Alternatively, a non-anticholinergic antiparkinsonian agent such as amantidine may be tried as an adjunct to the antipsychotic medication. In the case of akathisia, anticholinergic antiparkinsonian medications are unlikely to be helpful, but benzodiazepines are often useful (Benzodiazepines), and beta-blockers often work as well (Beta-Adrenoceptor Antagonists).

Switching from a "typical" (first-generation) antipsychotic agent to an "atypical" (second-generation) antipsychotic agent is another adjustment of the medication regimen to consider in cases of PPDDS (Siris ▸7) (▸Second and Third Generation Antipsychotics). The literature is inconsistent, but suggests that, in some cases, negative symptoms are reduced with second-generation antipsychotics (SGAs), and/or extrapyramidal side effects are lessened (Möller ▸6). There is also a literature suggesting, subject to a variety of methodological limitations, that rating scores for depression may be improved by the use of SGAs in schizophrenia (Möller ▸6). Indeed, SGAs have sometimes been touted as possessing augmenting antidepressant effects when used as adjunctive agents in patients with major depression.

There is also a role for adjunctive antidepressant medications in the treatment of PPDDS, particularly when extrapyramidal side effects have been ruled out (Siris and Bench ▸9) (Antidepressants). Patients must be maintained on adequate doses of antipsychotic medications when antidepressants are used, but the antidepressant drugs can gradually be raised to full therapeutic dosages. Vigilance should be maintained, however, for the pos-

sibility that the antipsychotic and the antidepressant might each interfere with the metabolism of the other, resulting in the possibility of adverse pharmacokinetic interactions (Drug Interactions), perhaps particularly when specific serotonin reuptake inhibitors (SSRIs) are involved (Möller ▸6). Although most of the controlled studies of adjunctive antidepressant use in PPDDS come from the era of first-generation antipsychotics (FGAs) and tricyclic antidepressants, the subsequent wide use of combinations including both FGAs and SGAs and a wide variety of more novel antidepressants nevertheless suggests both safety and utility for a variety of regimens (Siris et al. ▸10).

Although proper studies have not been done to support the use of lithium (lithium) or anticonvulsants (Mood Stabilizers) (Anticonvulsants) in PPDDS, it is rational to consider a trial of these agents, perhaps particularly in patients who manifest features of schizoaffective disorder, have a history of excitement or an episodic course as a component of their illness, or have family histories of affective disorders. Similarly, although there are not specific data to support it, ECT can be on the list of other treatments that might be useful in cases of PPDDS.

It is additionally important to provide adequate psychosocial support, increasing structure, reducing stress, and building skills, confidence, and self-esteem for patients during their treatment for PPDDS. This is particularly the case when the patient is suffering from a chronic disappointment reaction (demoralization syndrome) and needs to learn new strategies of thinking to foster success and happiness. However, proper psychosocial supports may be pivotal as well during pharmacological interventions because, from the patients' point of view, these interventions can literally change their world and they may need help in moving ahead from long-held, but now suboptimal, old ways of adapting to their old worlds toward new ways of productively adapting to their new worlds.

Conclusion

A syndrome of post-psychotic depressive disorder of schizophrenia (PPDDS) is commonly noted to occur in the residual phase of schizophrenia, after the resolution of florid psychotic symptoms. PPDDS can be a source of considerable morbidity, and even mortality, and consequently merits clinical attention.

The phenomenology of PPDDS may represent any one of a number of conceptually distinct states, including organic or medical factors, acute or chronic use, discontinuation of a variety of medications or substances, mood or parkinsonian side effects to antipsychotic medications, an expression of the "negative" symptoms of schizophrenia, an acute or chronic disappointment reaction, the prodrome of relapse into a new psychotic ep-

isode, an expression of schizoaffective disorder, or the expression of a diathesis of affective disorder distinct from the schizophrenia diathesis. In each case, appropriate psychopharmacologic and psychosocial management of the condition is crucial for preventing suffering and promoting functioning.

Cross-References

▸Anti-Parkinson Drugs
▸First-Generation Antipsychotics
▸Schizoaffective Disorder
▸Schizophrenia
▸Second and Third Generation Antipsychotics

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Pre-psychotic States and Prodromal Symptoms

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Synonyms

At-risk mental state
Pre-psychotic prodrome
▸Schizophrenia prodrome

Definition

The "prodromal phase" that precedes a first psychotic episode is a period characterized by increasing levels of nonspecific subthreshold symptoms associated with significant distress and growing functional impairment. This phase often continues for several years prior to the emergence of diagnostically-specific psychotic symptoms, with significant social disability becoming apparent well before the first psychotic episode. Because the psychotic disorders usually manifest during adolescence, a period of major developmental change, they may have particularly devastating consequences on lifetime functioning, highlighting the need for early intervention in order to minimize ongoing disability.

Role of Pharmacotherapy

The psychotic disorders occur at a frequency of around 2% in the general population and thus are relatively rare. However, their onset is most common during late adolescence and early adulthood, a period of life where critical developmental tasks are being accomplished in the psychological, social, educational, and vocational domains. Because serious mental illness substantially disrupts these processes and often leads to ongoing long-term disability, the early detection and treatment of people at risk of psychosis, before the onset of frank psychotic disorder, has long been a major goal in psychiatric practice.

The existence of a prodromal phase prior to a first episode of psychosis or a relapse of ▸schizophrenia was noted over a century ago, prompting the first calls for early treatment as a means of preventing serious illness and ongoing disability. However, until relatively recently, research into the possibilities for early intervention has been limited by the lack of effective treatments, as well as the widespread perception that the ongoing disability associated with the psychotic disorders was inevitable. Over the last decade the advent of more effective drugs, particularly the atypical antipsychotics,

and the development of better psychosocial treatments has led to the realization that good long-term outcomes are possible for patients and rekindled interest in the area of early intervention. An important result of this renewed research effort is a series of careful epidemiological studies that have enabled the characterization of the "psychosis prodrome", a significant advance which has finally allowed early therapeutic intervention in the psychotic disorders to become a real possibility. These research findings have now been translated into evidence-based clinical practice in a growing number of specialized early intervention services worldwide and have made a major contribution to the improved outcomes that are now expected for young people who are experiencing the onset of a psychotic illness (Yung et al. ▸10).

Retrospective studies of first-episode psychosis patients, examining the course of illness from the pre-morbid period through to the emergence of frank psychosis, have shown that the first episode is almost always preceded by a prodromal period of several years that are characterized by increasing levels of psychological symptoms, significant distress, and a marked decline in social and vocational functioning compared to pre-morbid levels. In general, negative symptoms such as decreased concentration, reduced drive, and lack of energy predominate early in the prodromal phase, accompanied by nonspecific symptoms including sleep disturbance, anxiety, and irritability. Affective symptoms, primarily depression, are also common. These symptoms tend to accumulate exponentially until relatively late in the prodrome, when subthreshold positive symptoms (psychotic symptoms) emerge. Ultimately, these positive symptoms intensify and culminate in the transition to frank psychosis. Typically, increasing levels of social and vocational disability accompany the increase in symptomatology, with significant disability becoming apparent well before the first psychotic episode. The degree of disability that develops during the prodromal period appears to set a ceiling for the extent of the eventual recovery, highlighting the need for early intervention (Yung et al. ▸10).

Because these prodromal symptoms, including subthreshold psychotic-like experiences, are nonspecific and occur frequently in the general population, especially among adolescents and young adults, they cannot be considered as diagnostic of a pre-psychotic state in their own right. Additional risk factors and specific criteria are necessary to exclude false positive cases in order to avoid unnecessary treatment and the stigma often associated with the diagnosis of a mental illness. In order to increase the prognostic specificity of these prodromal symptoms, two additional risk factors have been developed based on our clinical experience and the available epidemiological evidence, to add to the screening criteria. The first of these is being aged

between 14 and 30, since young people in this age range are at greatest risk of developing a psychotic disorder. The second is a need for clinical care, since young people who are not distressed by their symptoms and who have not experienced a decline in their functioning are less likely to become seriously unwell in the near future. A careful prospective study of a young, help-seeking population identified a subset of young people who appear to be at incipient risk of frank psychosis. The specific criteria defining this ultra-high risk (UHR) group fall into three groups (1) having experienced attenuated psychotic symptoms during the previous year; (2) having brief episodes of frank psychotic symptoms that resolve spontaneously over the previous year; and (3) having a schizotypal personality disorder, or a first degree relative with a psychotic disorder, and recently experiencing a significant decline in functioning (Table ▸1) (McGorry and Singh ▸4; Yung and McGorry ▸9). Up to 40% of the young people who met these UHR criteria made a transition to psychosis within the following year, a rate several hundred-fold greater than the expected incidence rate for first-episode psychosis in the general population. These criteria have since been validated in a series of international studies. However, it should be borne in mind that while they do identify a group of young people who are at incipient risk of psychosis, the identification itself is by no means a diagnosis per se; the majority of young people who fulfill the UHR criteria do not develop a full-threshold psychotic disorder.

Pre-psychotic States and Prodromal Symptoms. Table 1. Ultra High Risk criteria: (1) must be aged between 14 and 29 years, (2) have been referred to a specialized service for help, and (3) meet the criteria for one or more of the following three groups.

Group 1: Attenuated positive psychotic symptoms	• Presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behavior and appearance • Frequency of symptoms: at least several times a week • Recency of symptoms: present within the last year • Duration of symptoms: present for at least 1 week and no longer than 5 years
Group 2: Brief limited intermittent psychotic symptoms	• Transient psychotic symptoms. Presence of at least one of the following: ideas of reference, magical thinking, perceptual

(Continued)

	disturbance, paranoid ideation, odd thinking or speech • Duration of episode: less than 1 week • Frequency of symptoms: at least several times per week • Symptoms resolve spontaneously • Recency of symptoms: must have occurred within the last year
Group 3: Trait and state risk factors	• Schizotypal personality disorder in the identified individual, or a first-degree relative with a psychotic disorder • Significant decline in mental state or functioning, maintained for at least 1 month and not longer than 5 years • This decline in functioning must have occurred within the past year

The elaboration of operationalized criteria that significantly reduce the risk of inappropriate treatment has not only proven to be clinically useful, but has also catalyzed renewed efforts into developing effective early intervention strategies designed to prevent, or at least delay the onset of psychosis and other serious mental illness. Clearly, the young people who fulfill these UHR criteria have demonstrable clinical needs, and thus effective treatment is called for not only on human, but also on medical and ethical grounds. Current early intervention strategies range from the psychologically-based, including psychoeducation, supportive psychotherapy, cognitive behavioral therapy (CBT), and family work; to the biologically-based, including symptomatic treatment for depression, anxiety and any sub-threshold psychotic symptoms, through to experimental neuroprotective approaches. The global aim of treatment in the prodromal phase is to provide comprehensive clinical care designed to reduce presenting symptoms, and if possible, to prevent these symptoms from worsening and developing into an acute psychosis.

Currently Accepted Strategies for Treatment of Prodromal Symptoms

Studies have shown that around 25% of these at-risk young people have a concomitant diagnosis of depression, and that over 60% of UHR patients will experience a depressive disorder during their lifetime. Thus, treatment with cognitive behavior therapy and/or antidepressants, most commonly the SSRIs, may be indicated. These therapies are generally well-accepted and well-tolerated by this patient group, and lead to significant clinical im-

provement. Some preliminary evidence suggests that antidepressants may have a protective effect if initiated early enough in the illness process; effective treatment of depression may help to limit the development of negative symptoms and social withdrawal. Anxiety is also extremely common in this patient group, with around 25% of these young people having a current diagnosis of an anxiety disorder, while around 30% experiences an anxiety disorder in their lifetime. Benzodiazepines may be prescribed to relieve short-term anxiety and sleep disturbance and to reduce agitation. Because anxiety tends to increase as positive symptoms develop, effective treatment of anxiety may help to relieve the stress associated with any subthreshold psychotic symptoms that may be present, and allow the patient to better cope with social and vocational difficulties as they arise, limiting the functional decline that occurs during the prodromal period (Yung et al. ▸10).

Subthreshold psychotic symptoms are almost inevitably present in UHR patients. However, in general, antipsychotic treatment should be avoided if at all possible. Indications for antipsychotic treatment include rapid deterioration, hostility, and aggression that poses a risk to the patient or others, severe suicidality, or depression that does not respond to other treatments. Antipsychotics may also be trialed for patients who have not responded to psychosocial interventions and who are still unwell and functioning poorly. If medication is warranted, the atypical antipsychotics should be used on a trial basis for a limited time only, and at the lowest dose possible, to minimize the risk of extrapyramidal side effects (see below). If there is clinical benefit and resolution of symptoms after 6 weeks, the medication may be continued for a further 6 months to 2 years, with the consent of the patient (Yung et al. ▸10).

The atypical antipsychotics are the agents of first choice for young patients since they have been shown to be associated with fewer extrapyramidal side effects than the potent first-generation agents. Apart from the movement disorders, the major side effects reported for the atypical agents include significant weight gain and an increased risk of diabetes and metabolic disturbance. Other common side effects include sedation, fatigue, and decreased libido, and less commonly, prolactinemia and cardiac arrhythmias. In the few studies involving first-episode and prodromal patients that have been published so far, apart from weight gain, the other side effects reported have been relatively mild and/or transient, and thus the atypical antipsychotics appear to be well tolerated in this vulnerable patient group (International Early Psychosis Association Writing Group ▸2).

Experimental Strategies for Short-Term Symptomatic Treatment of Prodromal Patients

The safety and efficacy of two atypical antipsychotics, ▸amisulpride and ▸aripiprazole, for the relief of symptoms in young people at incipient risk of psychosis has been tested in two recent clinical trials. One of these involved a group of 124 young people, where participants received amisulpride (flexibly dosed at 50–800 mg/day) plus needs-based psychosocial support, or psychosocial support alone for a period of 12 weeks (Ruhrmann et al. ▸7). Regardless of their treatment group, participants were permitted to take citalopram for moderate to severe depression, and lorazepam, temazepam, or chloral hydrate for agitation or sleep disturbances, and if necessary, biperiden was prescribed for extrapyramidal symptoms. While both groups improved over the course of this study, the amisulpride group showed a reduction in symptoms that was at least double that of the control group across a range of measures designed to assess the levels of positive and negative symptoms, as well as general psychopathology. Both groups also showed an improvement in their levels of functioning, and again, this was significantly greater in the amisulpride group than in the control group. The final mean daily dose of amisulpride was 118.7 ± 10.7 mg, which was well within the lower end of the dose range. Four of 61 participants in the amisulpride group developed ▸akathisia, compared to 1 of 43 in the control group, with biperidin being prescribed for 3 of the 4 participants from the amisulpride group. The most frequent side-effects associated with amisulpride were related to a marked increase in prolactin levels, commonly seen in response to the benzamides, particularly when associated with an SSRI. As a consequence, transient menstrual disturbances emerged in 4 females, 1 developed a prolonged cycle, and 1 dropped out due to amenorrhoea. Two males developed erectile and ejaculatory dysfunction, and 1 other decreased desire and erectile dysfunction (Ruhrmann et al. ▸7).

In the second study, the safety and efficacy of 5–30 mg/day aripiprazole for symptomatic relief was been tested in an 8-week pilot trial of 15 young people experiencing attenuated positive symptoms (Woods et al. ▸8). All participants were permitted to continue any antidepressant, mood stabilizing, or stimulant medication that they had been prescribed, but not to begin new medications or change existing doses during the study period. However, lorazepam was allowed for anxiety or agitation, and benztropine was prescribed for extra-pyramidal symptoms, if necessary. Individual and family-centered psychosocial support was available for all participants.

At the end of the study, the mean daily dose of aripiprazole was 15.67 mg, and adherence to medication was over 90% for the entire study period. Eleven of the 15 participants were no longer experiencing positive symp-

toms, and all participants showed a significant improvement in their levels of positive, negative and general symptoms and in their overall functioning. Notably, while the 2 participants who completed the study without responding to aripirazole chose not to continue treatment, the remaining 11 participants elected to remain on medication. The most common adverse effect reported was emergent akathisia, which occurred in 8 participants, though this usually remitted after management, with 4 participants requiring benztropine at the end of the trial. Weight gain was minimal, with a mean of 1.2 kg gained over the trial period (Woods et al. ▸8).

Experimental Strategies Designed to Prevent the Onset of Psychosis

To date, only three clinical trials of pharmacological treatments specifically designed to prevent the onset of psychosis have been published. Our group ran the first of these trials, which aimed to test the efficacy of 6 months of low dose ▸risperidone treatment plus CBT in preventing the onset of psychosis in a group of 59 UHR young people recruited from within our clinical service (McGorry et al. ▸5). Participants were randomized to either the control group or the intervention group, with the control group receiving supportive psychotherapy and general case management. As well as these elements, the intervention group undertook a CBT program designed to develop an understanding of their symptoms, to learn strategies to enhance their control of these symptoms and to reduce associated distress. In addition, this group received 1–2 mg of risperidone daily for the 6 months of the treatment phase. Risperidone therapy was commenced at 1 mg/day then increased to 2 mg/day provided no adverse effects were experienced, and if necessary, the dosage was reduced to 1 mg/day. All participants were permitted to take sertraline for moderate to severe depression, and temazepam for insomnia.

At the end of the 6-month treatment phase, 3 of the 31 young people in the intervention group had developed frank psychosis, compared to 10 of the 28 in the control group. However, by the 12-month assessment another 3 patients in the intervention group had made a transition to psychosis, while no more transitions had occurred in the control group. Adherence to the CBT component was high, while adherence to risperidone therapy was variable; 13 patients were classed as non-adherent (<50% of doses taken), 4 as partially adherent (>50% of doses taken), while 14 were considered fully adherent (almost 100% of doses taken). Interestingly, only 1 of the patients considered fully adherent developed frank psychosis. Adverse effects were noted in only 4 patients; 1 developed minor rigidity and 3 experienced mild sedation, and all were relieved by lowering the dose of risperidone. The mean final dose was 1.3 ± 0.901 mg/day. Not surprisingly, the use of sertraline was lower in the intervention group (41.9%) than in the control

group (60.7%). Sertraline treatment did not affect the rate of transition to psychosis in the control group, since this was not significantly different in those who had been prescribed sertraline and those who had not (McGorry et al. ▸5).

Medium-term follow-up of our study cohort 3–4 years after initial assessment showed that a further 4 patients from the intervention group and 2 from the control group had become psychotic since their 12-month assessments, which indicates that the "window of vulnerability" in these UHR young people continues well beyond the first year after their presentation to a clinical service and initial treatment. Over 80% of all participants reported that they had sought professional help for psychological concerns since their 12-month assessment, and among those who had not developed frank psychosis, 70% of those in the control group and 54% of the intervention group had been prescribed either antidepressants or anxiolytics over this period, emphasizing the need for care in these young people who although not psychotic, are significantly compromised by their illness (Phillips et al. ▸6).

The second trial was designed to test the safety and efficacy of ▸olanzapine at doses of 5–15 mg/day in preventing the onset of psychosis in a group of 60 UHR young people (McGlashan et al. ▸3). Participants were recruited after referral by clinicians or in response to advertisements, and randomly assigned to either the olanzapine or the placebo groups. In this study, concomitant psychoactive medications were not allowed, and all participants had access to supportive psychosocial interventions as needed. The treatment phase ran for 12 months, and was followed by a 12-month follow-up period and a 6-month period of open-label olanzapine treatment for all patients who experienced a conversion to psychosis.

At the end of the 12-month treatment phase, 5 of the 31 participants who had received olanzapine treatment had become psychotic, compared to 11 of the 29 participants in the placebo group. All 5 patients from the olanzapine group who converted to psychosis did so within the first 4 weeks of the treatment phase, while the 11 patients from the placebo group who made this transition did so throughout the entire 12 months of the treatment phase. Those in the olanzapine group showed an improvement in their levels of positive symptoms that was not seen in the placebo group, while both groups showed an improvement in their overall levels of functioning. Notably, during the 12-month follow-up after all medication was ceased, positive symptoms worsened in both groups, with the participants from the former olanzapine group showing a statistically significant increase in the levels of positive symptoms experienced. During this period, 3 of the 9 patients remaining in the study from the former olanzapine group converted

to psychosis, while 2 of the 8 remaining placebo group patients developed psychosis. The only significant adverse effects associated with olanzapine treatment were fatigue and weight gain, with 29% of the participants in the olanzapine group reporting fatigue compared to 3% in the placebo group, and 61% of the olanzapine group showing weight gain compared to 17% in the placebo group. The mean weight gain in the olanzapine group was 8.79 ± 9.05 kg, or 12.7% of the mean body weight, while that in the placebo group was 0.3 ± 4.24 kg, in line with other studies in patients suffering from schizophrenia. However, this weight gain was not accompanied by changes in blood laboratory values suggesting an increased risk of cardiovascular disease or diabetes (McGlashan et al. ▸3).

A very recent study involved the use of omega-3 essential fatty acids (EFA) for indicated prevention of psychosis in a group of 81 UHR young people (Amminger et al. ▸1). Participants were randomized to either the placebo group or the EFA group, and underwent a 12-week trial of treatment with 1.2 g/day EFA (a balanced mix of 700 mg EPA + 480 mg DHA) and a 12-month follow-up period. All participants were offered the same psychosocial support package, and antidepressants and benzodiazepines were allowed for the treatment of depression and anxiety, if necessary. Significantly, at the end of the 12-month follow-up period, 2 of the 41 (4.9%) participants in the EFA group had made the transition to frank psychosis, compared to 11 of the 40 (27.5%) participants in the placebo group. Significant reductions in the levels of positive, negative, and general symptoms were seen in the EFA group, along with an increase in overall functioning, and most interestingly, these benefits were continued after the cessation of the 12-week intervention phase. Furthermore, the number needed to treat (NNT) of 4 calculated in this study compared favorably to the NNTs of 4 and 4.5 that were reported in the trials of the antipsychotics described earlier (McGlashan et al. ▸3; McGorry et al. ▸5). No adverse effects were reported in either group, while the high level of compliance (over 80%) and low withdrawal rate (6% overall) indicate that this intervention was very well accepted by the participants.

This extremely promising study is the first trial of a natural substance for the indicated prevention of psychosis and the alleviation of prodromal symptoms. The evident clinical benefits and the absence of side effects suggest that the omega-3 fatty acids may indeed be a viable alternative to antipsychotic medication, offering a similar degree of overall therapeutic gain without the potentially serious and often distressing side effects associated with these agents.

Given the marked symptomatic improvements seen in response to low doses of antipsychotic medication, these preliminary studies suggest that

the atypical antipsychotics may provide significant therapeutic benefits to prodromal patients, particularly those with subthreshold psychotic symptoms. Furthermore, these agents, either alone or in combination with CBT, may at least delay progression to full-blown psychosis in UHR patients. Their relatively favorable side-effect profiles means that at low doses the atypical antipsychotics were generally safe and well tolerated in this patient group; however, further large scale placebo-controlled trials are necessary to establish the risk/benefit ratio of these interventions before evidence-based treatment recommendations can be made for either the antipsychotic medications or more experimental neuroprotective agents such as the omega-3 fatty acids.

Conclusions

Current clinical experience indicates that young people experiencing prodromal symptoms, and in particular those at UHR of developing a psychotic disorder, should be treated with the aim of ameliorating their symptoms and preventing further deterioration in the course of their illness. The results of the few experimental trials that are currently available indicate that these young people may benefit from various therapeutic intervention strategies including cognitively-oriented psychotherapy and/or specific indicated prevention with low-dose atypical antipsychotic medication or neuroprotective agents such as the omega-3 fatty acids, and that treatment should be continued for longer than 6 months, given that these patients remain symptomatic and vulnerable to the onset of psychosis well after their initial detection and treatment. However, since the evidence for the use of antipsychotics in prodromal patients is still preliminary, their use has not yet been endorsed in routine clinical practice. At this stage, indicated prevention for the psychotic disorders remains a major goal for researchers in this area.

Apart from relieving the increasing distress and disability associated with prodromal symptoms, early intervention provides numerous other advantages to these vulnerable young people. Effective treatment allows them to remain in education, training, or employment, with minimal disruption due to illness and thus they maintain better levels of social functioning and a higher quality of life than might otherwise be expected. Early engagement in therapy means that even those who do become psychotic can be treated promptly without needing emergency or inpatient care, thereby avoiding the distress and trauma associated with psychiatric hospitalization. Finally, early intervention and effective treatment allows the best chance of a full social and functional recovery, the best possible outcome in both economic and human terms.

Cross-References

▸Antipsychotic Medication: Future Prospects
▸Schizophrenia
▸Second and Third Generation Antipsychotics

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Prochlorperazine

Definition

Prochlorperazine is an antipsychotic that acts as a dopamine D2 receptor antagonist. It is a piperazine-phenothiazine derivative. It has prominent antiemetic and anti-vertigo activity. It is used infrequently as an antipsychotic, but lower doses are used to treat severe nausea, vomiting, vertigo, and labyrinthine disorders.

Cross-References

▸First-Generation Antipsychotics

Prolactin

Definition

A peptide hormone released by the pituitary gland and with an important role in lactation. Many antipsychotic drugs increase the release of prolactin (hyperprolactinaemia) with associated side-effects such as infertility, and menstrual irregularities and galactorrhea. Dopamine normally regulates prolactin secretion and drugs that block dopamine in the pituitary gland cause hyperprolactinaemia.

Propranolol

Definition

Propranolol is an anxiolytic acting as a nonselective β-adrenergic receptor antagonist. Originally prescribed to treat hypertension and, subsequently, for the prevention and treatment of migraine, the use of propranolol has expanded due to its anxiolytic properties, so as to include treatment of specific forms of acute stress reactions such as performance anxiety. As an anxiolytic, propranolol is usually not administered chronically but only acutely, prior to specific panic and anxiety-inducing events. Furthermore, this drug is often prescribed in treating alcohol withdrawal-induced tremors and tachycardia and also in the treatment of antipsychotic-induced movement disorders. In addition to this, recent preclinical studies suggest that it may also hold promise for the treatment of some drug dependencies. The side effects of propranolol are usually mild and transient and include lightheadedness, depression, insomnia, nightmares, disorientation, nausea, decreased heart rate (bradycardia), and hypotension. Withdrawal symptoms

after abrupt termination of chronic therapy are usually mild but may include chest pain, increased heart rate (tachycardia), headache and trembling.

Pseudo-Hallucination

Definition

A subject experiencing "pseudo-hallucinations" retains the capacity to recognize that these "novel" experiences are transient and drug induced, as opposed to true hallucinations in which no such discernment is possible.

Psychoeducation in the Management of Schizophrenia

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Definition

In the management of schizophrenia the term "psychoeducation" was first used by Anderson et al., ▸1 for a family intervention that combined imparting information about schizophrenia with therapeutic elements. In the meantime, numerous psychoeducational intervention programs have been developed throughout the world. Psychoeducation for patients and for their relatives is considered as a specific basic psychotherapeutic intervention in schizophrenia. The German working group "Psychoeducation in the treatment of schizophrenia", an association of psychiatrists and clinical psychologists who are engaged theoretically as well as practically in psychoeducation, has defined psychoeducation as "systematic, structured, didactic information on the illness and its treatment, and which includes integrating emotional aspects in order to enable - patients as well as family members - to cope with the illness. Within the framework of psychotherapy, psychoeducation refers to the components of treatment where active communication of information, exchange of information among those afflicted, and treatment of general aspects of the illness are prominent". (Bäuml and Pitschel-Walz, ▸2).

Current Concepts and State of Knowledge

Today the vulnerability-stress-coping-model of schizophrenia (Zubin and Spring, ▸16) is a well-known and widely accepted theory. It assumes that the pathogenic effect of stressors can be reduced if a person who is vulnerable to schizophrenia knows how to deal with stress successfully and is supported by a stable social environment. The patient is not seen as a passive object, who is at the mercy of their illness, but as an active subject, who can become an expert in their illness and who can create conditions that permit a favourable development of the illness. One important condition precedent to a positive course of the illness is a good compliance. More than 50% of rehospitalisations may be attributable to patients' noncompliance with prescribed antipsychotics. Noncompliance can be related to lack of information, subjective attitudes concerning the illness and the medication, the stigma of taking medication, or adverse drug reactions. Psychoeducation is a successful strategy for enhancing coping strategies and to improve compliance with antipsychotics.

The vulnerability-stress-coping-model has also shown that it is necessary to involve the patient's family as the most important part of the patient's social environment and therefore it is necessary to instruct the patient's family on how to provide useful support. On the other hand, families with a member afflicted with schizophrenia may also feel burdened and need help in coping with this burden and the related personal stress.

Various intervention programs have been developed in the last 30 years that can be subsumed under the category of "psychoeducation" or at least contain psycho-education as an essential component, such as family psychoeducation in a single-family (e.g. Falloon et al., ▸5), or a multi-family setting (e.g. McFarlane, ▸8), or psychoeducational groups for patients and/or for relatives (see for example: Kissling et al., ▸6) with 8 to 12 participants on average.

The overall goals of these programs are to:

1. provide comprehensive information about the illness and the treatment options
2. formulate a functional concept of illness
3. improve compliance/adherence
4. develop and enhance coping strategies
5. establish techniques for crisis management
6. enhance self efficacy and empowerment
7. support emotional relief
8. improve subjective feeling
9. instil hope

And additionally for the families:

10. reduce the family members‘ anxiety about the patient
11. improve self confidence
12. enhance the ability to react constructively to the patient
13. reduce family burden

The duration of psychoeducational interventions vary depending on the program and its intensity (between 4 and 25 sessions; from several weeks up to two years). Interactive spreading of information and emotional relief are the basic elements of the psychoeducational concept. Psychoeducation usually includes information about the illness, symptoms, aetiology, causes, acute medical treatment and relapse prevention, psychosocial treatment, psychotherapy and self-help strategies, as well as sharing experiences with others for emotional relief. Table 1 shows the modules of a psychoeducational program that is often used in Germany (Kissling et al., ▸6).

Table 1: Modules of a psychoeducational program (Kissling et al. ▸6)

Session	Contents
1	Introduction, organisational questions, warming-up
2	Signs and symptoms of schizophrenia, diagnosis of schizophrenia
3	Causes of schizophrenia: dopamine hypothesis
4	Causes of schizophrenia: vulnerability-stress-coping model
5	Treatment: medication - effects and side-effects
6	Treatment: psychosocial support and psychotherapy
7	Relapse prevention, warning signs and emergency plans, role of the family
8	Self-help groups, literature, contact addresses, feedback, finishing the group

Brochures, books, and videos can be introduced in a supportive function when it comes to deepening and consolidating verbally transmitted contents. The employment of various forms of media can, however, never be misunderstood as substituting continual dialogical support.
Even though information plays an important role in psychoeducation (”knowledge is power”), the enhancement of empowerment and actively coping with the illness and dealing with emotional topics in the group are further essential components of psychoeducation that go beyond mere education. Emotional topics and their frequencies in psychoeducational groups are listed in Table 2.

Table 2: Frequency of emotional topics discussed in psychoeducational groups – answers of 130 psychiatric hospitals in Germany, Austria and Switzerland (Rummel-Kluge et al. ▸15)

Emotional topics	Frequency
Stigmatization	86%
Isolation	81%
Guilt and shame	70%
Suicidality	63%
Quarrel with destiny	56%
Burn-out	30%

In longer-term interventions, components as communication training, problem solving, early warning sign training and individualized emergency planning can be explained at length.

Information in the relatives' groups is of the same tenor as in the patients' groups and the relatives receive the same written material. In addition, there is discussion about how family members can better help the patient with schizophrenia and how they can obtain support and emotional relief for themselves. The psychoeducational family programs are no longer aetiology-oriented but are seen as a secondary prevention programme, i.e. they should help those concerned to cope better with schizophrenia and aim at improving the quality of life for all family members.

All these psychoeducational intervention approaches imply an optimal psychopharmacological treatment of the patient.

Efficacy

Many family interventions involve psychoeducation and many studies of psychoeducation involve family members. Pitschel-Walz et al., ▸13 performed a meta-analysis to examine the effects of family involvement in the management of schizophrenia. Twenty-five randomised intervention studies were included. Most of them evaluated a family psychoeducation program. The main study criterion was the patient's relapse rate, measured by either a significant worsening of symptoms or rehospitalisation in the first two years after an index hospitalisation. The meta-analysis clearly confirmed that the involvement of the family in the treatment of schizophrenia can reduce relapse and rehospitalisation rates by as much as 20 percentage points, i.e. an average relapse rate of 50% could be reduced to 30%, if the family is provided with extensive information and support from professionals. Family interventions that continued for more than three months were more effective than shorter interventions, i.e. short-term interventions such as one or two educational lectures for relatives are not sufficient to sub-

stantially influence the relapse rate or the course of the illness. Different types of comprehensive family interventions had similar results. The meta-analyses of Pilling et al. (▶12) and Pharoah et al. (▶11) confirmed the result that family interventions can decrease relapse and rehospitalisation rates and additionally showed that these interventions can improve medication adherence. Meta-analyses on psychoeducation (Pekkala and Merinder, ▶10; Lincoln et al., ▶7) reconfirmed the significant effect on the relapse rate as long as family members were included. In the meta-analysis of Lincoln et al. (▶7) psychoeducation directed at patients alone did not yield significant effects. To improve the results of patient psychoeducation they suggested offering patient psychoeducation in outpatient settings more frequently and to provide in the psychoeducational programs more psychotherapeutic support for the patients to transfer their knowledge into every day life.

Up to now, three studies have evaluated the long-term effects of psychoeducation with involvement of family carers (Bäuml et al., ▶3). Despite some differences in the study populations and the psychoeducational procedures, very similar rehospitalisation rates were found. According to the effect size calculation for 5 to 8 years, an average success rate difference of 29 percentage points concerning the rehospitalisation rates could be achieved. Thus, psychoeducation does not produce merely short-term effects, but is successful even on the long run. Besides the rehospitalisation rates the number of rehospitalisations and the number of hospital days could be reduced. Figure 1 shows the hospital days per patient with and without psychoeducation after one and after seven years according to the results of the study by Bäuml et al. (▶3).

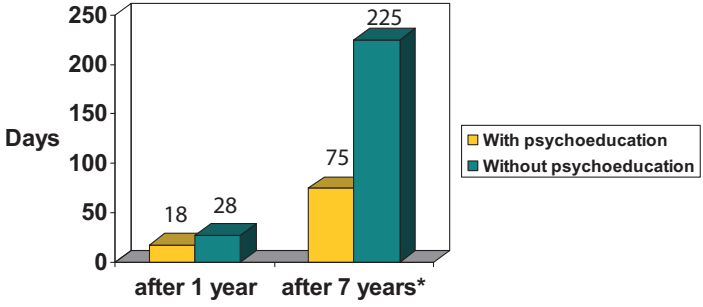

Figure 1 Hospital days per patient with or without psychoeducation (Bäuml et al., ▶3) * n = 48; t-test < 0.05

P

Because of its positive results, psychoeducation and especially family psycho-education is considered an integral part of the state-of-the-art treatment in many treatment guidelines for schizophrenia.

Dissemination

On consideration of the evidence base for family psychoeducation in schizophrenia, there is still an enormous gap between scientific findings and clinical reality. Even in countries where a lot of research into psychoeducation has been done such as USA, Spain or Germany fewer than 10% of family carers of patients with schizophrenia receive any support or psychoeducation (Dixon et al., ▸4; Montero, ▸9; Rummel-Kluge et al., ▸15). In Germany, Austria and Switzerland patient-directed approaches are much more frequent in clinical practice than family psychoeducation.
Nevertheless, only every fifth patient is included in a psychoeducational group. Thus an important opportunity is being missed to further improve the outcome of patients with schizophrenia.
Nevertheless, only every fifth patient is included in a psychoeducational group. Thus an important opportunity is being missed to further improve the outcome of patients with schizophrenia.
A number of different reasons might contribute to the current lack of psychoeducation. Known implementation barriers for psychoeducation are:

1. Workload (no time; no manpower)
2. Organisational reasons
3. Costs (for example: in some institutions family psychoeducation cannot be charged, as carers are considered healthy and therefore not eligible for therapeutic interventions)
4. Insufficient know-how
5. Reservation, scepticism towards the intervention

Peer-to-peer moderation may be a new strategy for increasing the number of potential moderators of psychoeducational groups. Rummel et al. (▸14) evaluated a training based on a 5-step curriculum for psychoeducational peer moderators and demonstrated that peer-to-peer psychoeducation is feasible and results may be comparable to psychoeducation conducted by mental health professionals.

Cost reduction through psychoeducation

Bäuml et al. (▸3) showed in their long-term study with a follow-up period of 7 years, that with a bifocal psychoeducational program for patients and their relatives it was possible to save about 37,500 euros per patient, given a rate of 250 euros per hospital day in the inpatient sector. By reducing the

number of days required, not only was the patients' and their carers' suffering alleviated, but the expenses for health care in general were reduced. Following a model calculation of Rummel-Kluge et al. (▸15) over 150 million euros in direct costs could be saved in Germany alone by tripling the number of patients and their relatives who are provided with a psychoeducational program.

Conclusion

In the coming decade, the study results need to be integrated into routine practice to enable as many patients as possible to benefit from these findings. Especially psychoeducational interventions for patients and their families should become a basic part of a comprehensive psychosocial package that is offered to all patients with schizophrenia. Researchers, patients and their families and those responsible for mental health service policy must work together to set the stage for a widespread and successful implementation of these interventions. The overall goal of all these scientific endeavours is the effective improvement of the long-term outcomes for patients suffering from schizophrenia.

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Psychotic Symptoms

Definition

Refers to a cluster of symptoms such as: paranoia, hallucinations, delusions, and incoherent speech and behavior.

Quetiapine

Definition

Quetiapine is a second-generation antipsychotic that acts as an antagonist at dopamine D2 and serotonin 5-HT2A receptors, with a generally broad receptor-binding profile. Quetiapine is indicated for the acute and maintenance treatment of schizophrenia and bipolar disorder. Because of its low propensity to cause extrapyramidal symptoms, the drug can be used to treat psychosis in Parkinson's disease. It is a dibenzothiazepine derivative that dissociates quickly from the D2 receptor. Fast-dissociating D2 antagonists have been hypothesized to allow dopamine to still interact with the D2 receptor under conditions of phasic bursts of dopamine release, thereby eliciting its normal effects in the nigrostriatal and tuberoinfundibular pathways and reducing the risk of side effects. Possibly because of these properties, the risk of extrapyramidal symptoms and effects on prolactin release is lower than for first-generation antipsychotics. Quetiapine has relatively prominent histamine H1 antagonistic effects that are likely to contribute to its sedative properties. The drug also has an active metabolite, norquetiapine.

Cross-References

▸Antipsychotic Medication: Future Prospects
▸Schizophrenia
▸Second and Third Generation Antipsychotics

Rating Scales and Diagnostic Schemata

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Synonyms

Assessments
Inventories
Measures
Tests

Definition

Diagnostic precision is achieved using structured diagnostic interviews. In contrast, rating scales are not intended for diagnostic purposes. Their function is to measure the severity of a condition or symptom cluster after the diagnosis is made by independent means. Typically, in psychopharmacology research, patients are screened into studies using structured diagnostic interviews. The response to treatment over time is then assessed by measuring the severity of the primary and associated symptom clusters or domains of interest from baseline through treatment follow-up (American Psychiatric Association ▸1).

Principles and Role in Psychopharmacology

Structured Diagnostic Interviews

Structured diagnostic interviews were developed to improve reliability in making psychiatric diagnoses for clinical and research purposes. Psychiatric diagnosis was very unreliable prior to the introduction of structured diagnostic interviews. Different criteria were used in different countries and within different schools of psychiatric thought. Within these groups, diagnosis varied based on the manner and on the amount of information elicited from patients. Information provided by patients was interpreted and assembled differently in reaching a diagnosis. The systems used to elicit information, to assemble this information, and to make diagnoses were too many, too varied, too inconsistent, and too divergent to permit accurate communication between large numbers of clinicians and to foster constructive and efficient international collaboration in research. The adoption of efficient and easily administered structured diagnostic interviews, that were translated into a large number of languages and used as consistent diagnostic criteria, has harnessed the energy of international research col-

laboration in pursuit of finding better treatments for, and understanding of, psychiatric disorders (Sheehan et al. ▸15; Spitzer et al. ▸16). Structured diagnostic interviews reduce variance in information gathering and reduce criterion variance in assembling this information to make a diagnosis. In this way, they improve both the reliability and quality of diagnostic decision-making.

Choice of Scales

A typical treatment-outcome study uses at least three scales: a scale to measure improvement in the symptom cluster of primary interest (Hamilton ▸8, ▸9; Montgomery and Asberg ▸11); another scale to measure the functional impairment or disability (Endicott et al. ▸5; Sheehan and Sheehan ▸14); and a third scale to measure the global improvement (Guy ▸7). In the past 2 years, the tracking of suicidality in psychiatric and neurological studies has also become routine and is now required by many regulatory agencies (Coric et al. ▸4; Posner et al. ▸12). Additional scales are frequently used to assess other secondary symptom clusters of interest, e.g., quality of sleep, ▸cognitive impairment (Folstein et al. ▸6), negative symptoms in ▸schizophrenia (Kay ▸10), anxiety symptoms in depression, or sexual symptoms. With the rise in managed care and increasing concern about cost containment, there is more inclusion of pharmaco-economic measures, especially on health care utilization and cost data. Since major drivers of costs in the management of many psychiatric disorders are poor adherence, increasing switch rates, and more augmentation with other medications, cost drivers are also increasingly tracked in long-term studies. A wide array of scales is available to assess adverse events. Examples include assessments of extrapyramidal side effects on antipsychotic medications (Barnes ▸2), assessments of sexual side effects with antidepressants (Clayton et al. ▸3), assessments of discontinuation withdrawal symptoms and of abuse liability, craving or "liking" with controlled substances (Selzer ▸13).

Scale Metrics

Psychometric constructs may be measured in two major ways. Categorical classification (e.g., yes or no) qualitatively assesses the presence of symptoms, signs, or attributes and is widely used in diagnostic assessment through structured diagnostic interviews. Continuous measures (e.g., height or weight) permit quantitative assessment of the severity, intensity, or frequency of symptoms, signs, or attributes. In between these two poles lie the ordinal scales that use an ordered set of categories (e.g., none, mild, moderate, and severe). Such ordinal scales are effectively treated and analyzed like continuous measures especially if they have 10 or more points. Continuous or ordinal scales that yield a total score may themselves be used

for categorical classification. For example, a score of seven or less on the Hamilton Depression Rating Scale (Hamilton ▸9) may be classified as a remission in depression.

A variety of scale structures or metrics are used in continuous or ordinal scales. The most common scale structure involves the use of a 5- or 10-point scale. Dichotomous categorical scales are less common and a few widely used scales have six or seven response options. Likert scaling is frequently used to measure change in symptoms in efficacy studies. Visual analog scales are popular in the assessment of pain. The DISCAN design metric is increasingly popular in scales designed to be sensitive to drug-placebo differences (Sheehan and Sheehan ▸14). Although measures of frequency, e.g., of panic attacks, of seizures, or of tics are often used as outcome measures; in general, they disappoint in their ability to discriminate between active and placebo treatments. The main reason is that the frequency of most behaviors is of skewed distribution in nature. Non-parametric tests statistically punish sensitivity and this price makes them less able to discriminate drug from placebo and to be less sensitive to change.

Scale Testing

Scales and structured interviews in psychopharmacology must be subjected to proper reliability and validity testing. Validity tests the degree to which the scale or structured interview is consistent with a "gold standard" measure (e.g., how well a structured diagnostic interview maps the diagnostic classification or how a severity scale accurately reflects the severity of a disorder). The problem in psychiatry is that the "gold standard" is not really "gold". Three kinds of reliability testing are usually done on scales and structured interviews. These include inter-rater reliability, test-retest reliability, and internal consistency. Inter-rater reliability measures the agreement between two raters in rating the same subjects using the same scale or interview at the same time. It is most useful in assessing clinician-rated scales. Test-retest reliability measures the agreement between assessments done at two different points in time (e.g., the same scale done on consecutive days, but assessing the same time period). It has special value in assessing self-rated scales. Internal consistency measures the agreement among the items within a scale. It assesses the degree to which all the items measure a single dimension.

In spite of the limitations of these paper and pencil interview tests, they have performed well in guiding our search for and selection of effective treatments. Researchers in psychopharmacology continue to refine their precision and predictive value. Some day, they will be largely replaced by more precise laboratory tests.

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Rehabilitation in Schizophrenia

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Introduction

There is no cure for schizophrenia. Thus, the treatment of schizophrenia rests pragmatically on three main pillars. Firstly, there are medications to relieve symptoms and prevent relapse. Secondly, psychosocial interventions help patients and families to cope with the illness and aim at preventing relapse. Thirdly, rehabilitation helps patients to reintegrate into the community and regain occupational functioning.

Goals and Objectives of Rehabilitation

The goal of psychiatric rehabilitation is to help individuals with persistent and serious mental illness to establish the emotional, social and intellectual skills needed to live, learn and work in the community with the least amount of professional support. Even though, psychiatric rehabilitation does not deny the existence or the impact of mental illness, rehabilitation practice has changed the perception of mental illness. Enabling persons with persistent and serious mental illness to live a normal life in the community causes a shift away from a focus on an illness model towards a model of functional disability. As such, other outcome measures apart from clinical conditions become relevant. Especially social role functioning including social relationship, work and leisure as well as quality of life and family burden is of major interest for the mentally disabled individuals living in the community.

Target population

The majority of the chronically mentally ill targeted by psychiatric rehabilitation have the diagnosis of schizophrenic disorders. The core group is drawn from patients with

- persistent psychopathology
- marked instability characterized by frequent relapse and
- social maladaptation

Up to 50 of these persons carry dual diagnoses especially in combination with substance abuse. The so-called young adult chronic patients constitute an additional category that is diagnostically more complicated. Many of them also have a history of attempted suicide. All in all they represent an utmost difficult-to-treat patient population.

Conceptual Framework

The overall philosophy of psychiatric rehabilitation in psychiatric disorders comprises two intervention strategies: the first strategy is individual-centred and aims at developing the patient's skill in interacting with a stressful environment. The second strategy is an ecological approach and is directed towards developing environmental resources to reduce potential stressors. Most disabled persons need a combination of both approaches.

In any event the starting point for an adequate understanding of rehabilitation is that it is concerned with the individual person in the context of his or her specific environment. Psychiatric rehabilitation is regularly carried out under real life conditions. Thus rehabilitation practitioners have to take into consideration the realistic life circumstances that the affected person is likely to encounter in their day-to-day living (Bachrach, ▸2).

A necessary second step is helping disabled persons to identify their personal goals. This is not a process where those persons simply list their needs. Motivational interviews provide a more sophisticated approach to identify the individuals' personal costs and benefits associated with the needs listed. This makes it also necessary to assess the individuals' readiness for change. Subsequently the rehabilitative planning process focuses on the patient's strengths (Bachrach, ▸2). This leads to a closely related concept: the aim of restoring hope to people who suffered major setbacks in self-esteem because of their illness.

Psychiatric rehabilitation cannot be enforced. Quite the contrary, psychiatric rehabilitation concentrates on peoples' rights as a respected partner and endorses their involvement and self-determination concerning all aspects of the treatment and rehabilitation process. These rehabilitation values are also incorporated in the concept of recovery. Within the concept of recovery, the therapeutic alliance plays a crucial role in engaging the patient

in his or her own care planning. It is essential that the patient can rely on his or her therapist's understanding and trust as most of the chronically mentally ill and disabled persons loose close, intimate and stable relationships in the course of the disease. Recent research has suggested that social support is associated with recovery from chronic diseases, greater life satisfaction and enhanced ability to cope with life stressors. Corrigan and colleagues (▸5) have found that the most important factor facilitating recovery is the support of peers. Therefore, psychiatric rehabilitation is also an exercise in network building.

Finally, people with mental disorders and their caregivers prefer to see themselves as consumers of mental health services with an active interest in learning about psychiatric disorders and in selecting the respective treatment approaches. Consumerism allows the taking of the affected persons' perspective and seriously considering courses of action relevant for them. In this context physicians should also acknowledge that disagreement about the illness between patient and him or her is not always the result of the illness process.

Current Approaches

Individual-centred psychiatric rehabilitation

Certain specific psychosocial measures commonly applied in the context of rehabilitation such as cognitive behavioural therapy, family therapy, psychoeducation, and cognitive remediation are discussed in separate chapters of this volume and will therefore not be covered here.

Pharmacological treatment from a rehabilitative perspective

Antipsychotic medication has proven useful in reducing, and often eliminating, acute symptoms of schizophrenia such as hallucinations and delusions. In addition, maintenance treatment is essential to prevent recurrence of symptoms and to protect the brain from the cognitive decline associated with relapse. The interactions between medication and psychosocial interventions appear to be more than merely additive, since each can enhance the effects of the other. Recent studies using newer antipsychotics suggest that these agents improve the participation of patients in psychosocial treatments (Marder, ▸11).

There is evidence of a neuroprotective effect of medication adherence, which has implications for prognosis and long-term cognitive functioning (Lieberman et al., ▸10). But adherence to antipsychotic medication is often poor. Within a year, 50 of patients started on medication will quit treatment, and virtually all stop medication within 2 years or take medication only

sporadically. Non-adherence is associated with psychotic relapse, hospitalization and other adverse outcomes.

Pharmacotherapy in psychiatric rehabilitation needs some special consideration. Symptom control does not necessarily have the highest priority as some side effects of pharmacological treatment can weaken a person's ability to perform his social roles and impair vocational rehabilitation. As such, it is no surprise that non-adherence with medication-taking is one of the most serious problems in the long term treatment of persons with serious mental illness. Many patients living in the community want to take responsibility for their medication themselves. Training in self-management of medication emphasizes patients' autonomy and increases acceptance of and responsibility for treatment. This also includes the varying of medication without consultation within certain limits.

Most interventions to enhance adherence have been pragmatic. A variety of strategies have been tested to improve medication adherence. Many studies tested the effects of patient education on enhancing adherence in patients with schizophrenia using group and individual educational methods. But research provides only mixed support for educational approaches (Dixon et al., ▸6). Interventions based on motivational interviewing and cognitive behavioral therapy seems to be promising as well as the provision of environmental support for medication adherence (Dixon et al., ▸6). However, at this point, there is insufficient evidence to recommend any specific intervention to promote adherence to antipsychotic medications among persons with schizophrenia (Dixon et al., ▸6).

Social skills training

In recent years, social skills training in psychiatric rehabilitation has become very popular and has been widely promulgated. The most prominent proponent of skills training is Robert Liberman who has designed systematic and structured skills training since the mid 70s (Liberman, ▸9). Liberman and his colleagues packaged the skill training in the form of modules with different topics. The modules focus on medication management, symptom management, substance abuse management, basic conversational skills, interpersonal problem solving, friendship and intimacy, recreation and leisure, workplace fundamentals, community (re-)entry and family involvement. Each module is composed of skill areas. The skills areas are taught in exercises with demonstration videos, role-play and problem solving exercises and in vivo and homework assignments (Liberman, ▸9).

The results of several controlled studies suggest that disabled individuals can be taught a wide range of social skills (Kurtz and Mueser, ▸8). Social and community functioning improve when the trained skills are relevant for the patient's daily life and the environment perceives and reinforces the

changed behavior. Unlike medication effects, benefits from skills training occur more slowly. Furthermore, long term training has to be provided for positive effects. Overall, social skills training have been shown to be effective in the acquisition and maintenance of skills and their transfer to community life.

Developing environmental resources

As a general rule people with psychiatric disabilities tend to have the same life aspirations as people without disabilities in their society or culture. They want to be respected as autonomous individuals and lead a life as normal as possible. As such they mostly desire (i) their own housing, (ii) an adequate education and a meaningful work career, (iii) satisfying social and intimate relationships, and (iv) participation in community life with full rights (Rossler, ▸14).

Housing

The objective of psychiatric reforms since the mid 50s of the 20th century has been to resettle chronically mentally ill persons from large custodial institutions to community settings. Providing sheltered housing in the community for the long-term patients of the old asylums was one of the first steps in the process of deinstitutionalisation. Most long-stay patients can successfully leave psychiatric hospitals and live in community settings.

Ideally, a residential continuum (RC) with different housing options should be provided. RC ranges from round-the-clock staffed sheltered homes to more independent and less staffed sheltered apartments which eventually allow individuals moving to independent housing in the community. Critics of RC contended that (i) up to date RC is rarely available in communities, (ii) that RC does not meet the varying and fluctuating needs of persons with serious mental illnesses, and (iii) that RC does not account for individuals preferences and choices. Supported housing, i.e. independent housing coupled with the provision of support services emerged in the 1980s as an alternative to RC. Supported housing offers flexible and individualised services depending on the individual's demands. In the meantime rehabilitation research could demonstrate that supported housing is a realistic goal for the majority of people with psychiatric disabilities. Once in supported housing the majority stay in housing and are less likely to become hospitalised. Other outcomes do not yield consistent results (Rog, ▸13).

Work

The beneficial effects of work for mental health have been known for centuries. Therefore, vocational rehabilitation has been a core element of psychiatric rehabilitation since its beginning. Vocational rehabilitation is

based on the assumption that work does not only improve activity, social contacts etc., but may also promote gains in related areas such as self-esteem and quality of life, as work and employment are a step away from dependency and a step to integration into society. Enhanced self-esteem in turn improves adherence to rehabilitation of individuals with impaired insight.
Vocational rehabilitation originated in psychiatric institutions where the lack of activity and stimulation led to apathy and withdrawal of their inpatients. Long before the introduction of medication occupational and work therapy contributed to sustainable improvements in long-stay inpatients. Today, occupational and work therapy are not any longer hospital-based but represent the starting point for a wide variety of rehabilitative techniques teaching vocational skills.
Vocational rehabilitation programs in the community provide a series of graded steps to promote job entry or re-entry. For less disabled persons brief and focused techniques are used to teach how they can find a job, fill out applications and conduct employment interviews. In transitional employment a temporary work environment is provided to teach vocational skills, which should enable the affected person to move on to competitive employment. But all too often the gap between transitional and competitive employment is so wide that the mentally disabled individuals remain in a temporary work environment. Sheltered workshops providing pre-vocational training also quite often prove a dead end for the disabled persons.
One consequence of the difficulties in integrating mentally disabled individuals into the common labour market has been the steady growth of cooperatives, which operate commercially with disabled and non-disabled staff working together on equal terms and sharing in management. The mental health professionals work in the background providing support and expertise.
Today, the most promising vocational rehabilitation model is supported employment (SE). The work of Robert Drake and Deborah Becker decisive influenced the conceptualization of SE. In their "Individual Placement Model" disabled persons are placed in competitive employment according to their choices as soon as possible and receive all support needed to maintain their position (Bond, ▸3). The support provided is continued indefinitely. Participation in SE programs is followed by an increase in the ability to find and keep employment (Cook et al., ▸4). Links were also found between job tenure and non-vocational outcomes, such as improved self-esteem, social integration, relationships and control of substance abuse (Bond, ▸3). It was also demonstrated that those who had found long-term employment through SE had improved cognition, quality of life and better symptom control (Bond, ▸3).

Although findings regarding SE are encouraging, some critical issues remain to be answered. Many individuals in SE obtain unskilled part-time jobs. Since most studies only evaluated short (12-18 months) follow-up periods, the long-term impact remains unclear. Currently we do not know which individuals benefit from supported SE and which do not (Bachrach, ▸2). After all we have to realize that the integration into the labor market does by no means only depend on the ability of the persons affected to fulfill a work role and on the provision of sophisticated vocational training and support techniques but also on the willingness of society to integrate its most disabled members.

Coordinating community services

Effective psychiatric rehabilitation requires individualized and specialized treatment, which has to be embedded in a comprehensive and coordinated system of rehabilitative services. But even when a variety of services are available, they are poorly linked in many cases, and costly duplication may occur.

While developing community support systems it became obvious that there is a need to coordinate and integrate the services provided as each involved professional concentrates on different aspects of the same patient. Therefore, as a key coordinating and integrating mechanism, the concept of case management (CM) originated. CM focuses on all aspects of the physical and social environment. The core elements of CM are the assessment of patient needs, the development of comprehensive service plans for the patients and arrangement of service delivery.

Over the past two decades a variety of different models of CM have been developed which exceed the original idea that CM mainly intends to link the patient to needed services and to coordinate those services. Today, most clinical case managers also provide direct services in the patient's natural environment. This model is called Intensive Case Management (ICM). ICM on its part is difficult to distinguish from Assertive Community Treatment (ACT).

Stein and Test have developed the basic compounds of ACT in the 1970's. The original program was designed as a community based alternative to hospital treatment for persons with severe mental illnesses. A comprehensive range of treatment, rehabilitation and support services in the community is provided through a multidisciplinary team. ACT is characterized by an assertive outreach approach i.e. interventions are mainly provided in the natural environment of the disabled individuals.

Research on CM and ACT yielded "mixed" results. While the traditional office-based CM approach obviously is less successful, the ACT model was found to be more beneficial when compared with standard care (Marshall,

▸12). ACT can reduce time in hospital, but has moderate or only little effects on improving symptomatology and social functioning. The differing features of the respective services might explain the international variation. Six regularly occurring features of successful services were identified: smaller case loads, regularly visiting at home, a high percentage of contacts at home, responsibility for health and social care, multidisciplinary teams and a psychiatrist integrated in the team.

Relationships

As a consequence of deinstitutionalisation the burden of care has increasingly fallen on the relatives of the mentally ill. Informal caregiving significantly contributes to health care and rehabilitation. Fifty to ninety per cent of disabled persons live with their relatives following acute psychiatric treatment. This is a task many families do not choose voluntarily. Caregiving imposes a significant burden on families. Those providing informal care face considerable adverse health effects, including higher levels of stress and depression, and lower levels of subjective well being, physical health and self-efficacy. Additionally, not all families are equally capable of giving full support for their disabled member and not willing to replace insufficient health care system. Caregivers regularly experience higher levels of burden when they have poor coping resources and reduced social support. But families also represent support systems, which provide natural settings for context-dependent learning important for recovery of functioning. As such, there has been a growing interest in helping affected families since the beginning of care reforms.

One area of interest deals with the expectations of relatives concerning the provision of care. Relatives quite often feel ignored, not taken seriously and also feel insufficiently informed by health professionals. They also may feel that their contribution to care is not appreciated or that they will be blamed for any patient problems. It certainly is no surprise that there is a lot of frustration and resentment among relatives considering the physical, financial and emotional family burden.

Reducing this burden is part of the scope of family therapies which are reviewed in the respective chapter.

We have to be aware that most family interventions were developed in the context of western societies during deinstitutionalization. Family caregiving might be quite different in a different cultural context. This refers to other cultures in total as well as to minority groups in western societies.

Participation in community life with full rights

As practitioners we often are confronted with the deleterious effects of stigma and discrimination in the lives of people with serious mental illnesses.

Numerous studies have examined stigmatizing attitudes toward people with mental illness (Angermeyer and Matschinger, ▸1; Grausgruber et al., ▸7). In recent years, the scientific interest in the perspective of the labeled individual has increased too. There is extensive empirical evidence of the negative consequences of labeling and perceived stigmatization. These include demoralization, low quality of life, unemployment and reduced social networks. Once assigned the label 'mental illness' and having become aware of the related negative stereotypes, the affected individuals expect to be rejected, devaluated or discriminated against. This vicious cycle decreases the chance of recovery and normal life.

On the other hand, well-integrated people with mental illness exhibit better outcomes regarding psychopathology and quality of life. The importance of social integration is underlined even more when considering the subjective availability of support: perceived social support predicts outcome in terms of recovery from acute episodes of mental illness, community integration, and quality of life.

On the basis of comprehensive research in this area during the last decade, several strategies have been developed to fight the stigma and discrimination suffered by those who have mental illnesses. Different research centres developed interventions directed to specific target groups relevant for destigmatization e.g. students or police officers. Persons in contact with mentally ill individuals quite often have a more positive attitude. Contact with the mentally ill persons also reduces social distance, which is a strong argument in favour of community psychiatry. Other initiatives have targeted stigma by means of more comprehensive programs. The World Psychiatric Association launched one of the internationally best-known programs in 1996 (www.openthedoors.com). All these initiatives makes clear that efforts in re-integrating persons with serious mental illness into community life must be accompanied by measures on the societal level.

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Reserpine

Definition

Reserpine is an indole alkaloid with antipsychotic and antihypertensive properties. It is currently not in clinical use for psychiatric conditions. Re-

serpine was isolated in 1952 from the dried root of *Rauwolfia serpentina* (Indian snakeroot), which was used in India for centuries to treat insanity and high blood pressure. Reserpine blocks the vesicular monoamine transporter, thereby acutely inhibiting the reuptake of the monoamines into the synaptic vesicles and increasing monoamine concentrations in the synaptic cleft, but eventually leading to depletion of vesicular monoamine stores in synaptic nerve endings upon chronic use, as the neurotransmitters that cannot reenter the vesicles will be degraded by monoamine oxidase. Chronic treatment can lead to depression, possibly due to depletion of these neurotransmitter stores. The drug can cause a range of additional side effects, for example, in the gastrointestinal tract (ulcerations, cramps, diarrhea) or the cardiovascular system (hypotension, bradycardia), all of which make it obsolete as an antipsychotic for today's treatment of ▸schizophrenia or other psychoses. It was also used as a tool in experimental pharmacology, to deplete stored neurotransmitters and thus allow tests of their roles in pharmacological reactivity; this usage ended when more selective drugs became available.

Cross-References
▸Schizophrenia

Risperidone

Definition
Antipsychotic drug of the second generation, atypical category with combined dopamine D2/serotonin2 receptor-blocking properties.

Cross-References
▸Second and Third Generation Antipsychotics
▸Schizophrenia

Schizoaffective Disorder

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Definition

There is no agreement about how schizoaffective disorders could be defined. According to the World Health Organisation (WHO) and its International Classification of Mental and Behavioral Disorders (ICD-10), schizoaffective disorders are "episodic disorders in which both affective and schizophrenic symptoms are prominent but which do not justify a diagnosis of either schizophrenia or depressive or manic episodes". The diagnostic criteria are the following:

G1	The disorder meets the criteria of one of the affective disorders (F30, F31, F32) of moderate or severe degree, as specified for each category.
G2	Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks: Thought echo, thought insertion or withdrawal, thought broadcasting. Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations. Hallucinatory voices giving a running commentary on the patient's behavior or discussing the patient between themselves, or other types of hallucinatory voices coming from some part of the body. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory, e. g. has visited other worlds; can control the clouds by breathing in and out; can communicate with plants or animals without speaking. Grossly irrelevant or incoherent speech, or frequent use of neologisms. Intermittent but frequent appearance of some forms of catatonic behavior, such as posturing, waxy flexibility and negativism.
G3	Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode.

(Continued)

	Symptoms from both G1 and G2 must be prominent in the clinical picture.
G4	*Most commonly used exclusion clause*. The disorder is not attributable to organic mental disorder or to psychoactive substance-related intoxication, dependence or withdrawal.

ICD-10 defines three different types of schizoaffective disorders: manic type (F25.0), depressive type (F25.1) and mixed type (F25.2).

The American Psychiatric Association (APA) in the fourth revision of its Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines the following diagnostic criteria for schizoaffective disorder:

A	An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia.
B	During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.
C	Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.
D	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

DSM-IV specifies two subtypes: bipolar type, if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes), and depressive type, if the disturbance only includes major depressive episodes.

While the main problem with the ICD-10 definition of schizoaffective disorders is their longitudinal aspect, the problem with DSM-IV concerns both – cross-sectional and longitudinal aspects. The problem with the cross-sectional definition of DSM-IV concerns the time span indicated in criterion B (during the period of illness there have been delusions or ▸hallucinations for at least 2 weeks in the absence of prominent mood symptoms). Obviously, that is an attempt of DSM-IV to separate schizoaffective disorders from psychotic mood disorders. The DSM-IV definition of mood disorders is broad, including even those with mood incongruent symptoms (even ▸first-rank schizophrenic symptoms). The chronological criterion, however, is rather arbitrary (2 weeks of psychotic symptoms without mood disorders is schizoaffective; less than 2 weeks is psychotic mood disorder!). Yet, the beginning of a psychotic episode is hard to assess exactly. Every

clinician knows that there is usually a gap of many days, weeks, or months between the beginning of a psychotic episode and admission to hospital. Reconstruction of the psychopathological picture, retrospectively, is fraught with difficulties. Given the likelihood that the psychotic period is underestimated, many patients who are really schizoaffective could be diagnosed as schizophrenic or as having psychotic mood disorder.

Furthermore, the intensity of both concurrent syndromes (mood and schizophrenic syndromes) can vary enormously during an episode; hence, it seems arbitrary to give chronological priority to the psychotic symptoms over the mood component. It is strange that DSM-IV rejected Jasper's hierarchical diagnostic principle, which suggested a diagnostic superiority of schizophrenic symptoms over affective symptoms, but, regarding the chronological criterion of the schizoaffective definition, obviously made an exception!

Considering what is known so far about schizoaffective disorders (see overviews in Marneros and Tsuang ▸5, ▸6), we suggest that the definition of schizoaffective disorders should contain two components: a cross-sectional and a longitudinal aspect.

The *cross-sectional* definition should be the definition of an episode; while the longitudinal definition should be that of a disease or disorder. The cross-sectional definition of a schizoaffective episode should be based on the simultaneous occurrence of symptoms of a schizophrenic and a mood episode, independent of the chronological manifestation. Thus, we agree with the definition of ICD-10, which yields three types of schizoaffective episodes: schizodepressive, schizomanic and mixed ones.

The *longitudinal definition* of schizoaffective disorder should consider the sequential occurrence of mood and schizophrenic episodes during course. The longitudinal research demonstrates that the course of schizoaffective disorders can be very unstable because schizoaffective episodes, pure mood episodes, and pure schizophrenic episodes can each occur at different points in the patient's longitudinal course.

What are such disorders when viewed longitudinally? Are they considered to be mood disorders because of the pure mood episodes, or schizophrenic disorders because of some pure schizophrenic episodes, or schizoaffective disorders because of some schizoaffective episodes? Relevant to this question is the finding that there are no differences between patients who have only had schizoaffective episodes, and those in whom schizoaffective episodes occur along with pure mood and schizophrenic episodes. There are therefore no differences between the *"concurrent"* and the *"sequential"* type of schizoaffective disorder. Patients, who change from pure mood episodes to pure schizophrenic episodes and vice versa, do not differ from patients

having schizoaffective episodes. In this sense, Marneros et al. suggest a longitudinal definition of schizoaffective disorders, including a concurrent and a sequential type, the *"concurrent type"* being characterized by the coincidence of schizophrenic and affective episodes and the *"sequential type"* being characterized by the longitudinal change from schizophrenic to affective episodes and vice versa (Marneros et al. ▸8).

How essential it is to have a longitudinal definition of schizoaffective disorder is illustrated by the Halle Bipolarity Longitudinal Study (HABILOS), in which the investigators tried to allocate disorders with manic symptomatology to "pure mood disorders" or to "schizoaffective disorders" according to DSM-IV, ICD-10 and the "empirical definition" as described above. Applying the ICD-10 definition, only 8.3% of the 277 patients could longitudinally be allocated to schizoaffective bipolar disorder and 36.1% to affective bipolar disorder, while the majority of patients (55.6%) could not be allocated longitudinally due to the occurrence of different types of episodes (schizophrenic, schizoaffective, affective) at different times.

Using the empirical definition with its cross-sectional and sequential aspects, however, all patients can be allocated: 36.1%, as in the ICD-10 categorization, could be allocated to bipolar mood disorder, and 63.9% could be allocated to schizoaffective disorder.

Recent research has confirmed earlier assumptions that schizoaffective disorders occupy a position between affective and schizophrenic disorders with regard to relevant sociodemographic and premorbid features, as well as with regard to patterns of course, outcome, treatment response and prophylaxis (Marneros et al. ▸7, ▸8).

It seems certain that schizoaffective disorders are not simply a type of schizophrenic disorder, although in some cases that are schizo-dominant the relationship to schizophrenia is quite clear. With respect to the relationship between schizoaffective and mood disorders, the similarities are more compelling than the differences (Marneros and Tsuang ▸5, ▸6).

Role of Pharmacotherapy

Although the clinical relevance of schizoaffective disorders is - inspite of controversies - meanwhile well established their treatment has received less attention in pharmacological studies, especially double blind studies, than other psychotic or non-psychotic major mental disorders. One of the main reasons might be the problem of their definition and, most important for the pharmaceutical industry, the clinical fact that schizoaffective disorders usually need a combined treatment with more than one substance, for example, with antipsychotics, antidepressants and mood stabilizers. Pharmacological studies dealing with schizoaffective disorders mostly investigated them as a subgroup of schizophrenia and seldom as a subgroup of mood

disorders. Pharmacological studies only on schizoaffective disorders are rare. Nevertheless it can be said that schizoaffective disorders are the domain of antipsychotics and mood stabilizers (Baethge ▸1; Jäger et al. ▸3; Levinson et al. ▸4; McElroy et al. ▸9; Mensink and Slooff ▸10).

All antipsychotics seem to be efficient in the treatment of schizoaffective disorders, but some atypical antipsychotics like ▸olanzapine, ▸quetiapine, ▸risperidone, or ▸ziprasidone are superior or have some advantages in comparison to typical ones. The heterogeneity of the studies and the investigated populations do not permit a science-based statement on the topic. The clinical effectiveness of mood stabilizers like lithium, carbamazepine or valproate was reported in some, however, heterogeneous studies. Clinical reality is compatible with such a conclusion.

Pharmacotherapy depends from the type of schizoaffective disorder. The official types of schizoaffective disorder registered in ICD-10 are: manic type, depressive type, mixed type, and those in DSM-IV are bipolar type and depressive type. Empirical work and longitudinal investigations considering a course of the disorder over many years, however, support some more subtypes:

(a) Schizo-dominant type
(b) Affective dominant type
(c) Bipolar type
(d) Unipolar type
(e) Sequential type

In the schizo-dominant type the main medication must be an antipsychotic one. In the affective dominant type mood stabilizers and antidepressants or antipsychotics are effective. The bipolar type is treated with antipsychotics combined with mood stabilizers, whereas the unipolar type needs to be treated with antipsychotics and antidepressants. The sequential type is totally ignored. The reasons are given at the beginning of this chapter. It is characterized by the occurrence of schizophreniform or mood episodes during course. The treatment focuses on the treatment of the particular disorder. The longitudinal treatment is a prophylactic one, mainly with mood stabilizers and antipsychotics (McElroy et al. ▸9; Mensink and Slooff ▸10).

Clinical studies reported also a positive effect of electroconvulsive treatment (Swoboda et al. ▸11). Other treatments like augmentation with l-thyroxine found only small benefit (Bauer et al. ▸2). The role of psychological treatment in schizoaffective disorders has not yet been systematically investigated.

Conclusions

Schizoaffective disorder is a very common diagnosis in clinical practice, but not sufficiently investigated, especially with regard to treatment.

Cross-References

▸Schizophrenia

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Schizophrenia

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Synonyms

Dementia praecox

Definition

Schizophrenia is a severe and persistent debilitating psychiatric disorder consisting of disturbances in thoughts, cognition, mood, perceptions, and relationships with others. According to DSM-IV-TR (American Psychiatric Association ▸1), the patient must have experienced at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms. Only one symptom is required if the delusions are bizarre or if auditory hallucinations occur in which the voices comment in an ongoing manner on the person's behavior, or if two or more voices are talking with each other. The patient must experience at least 1 month of symptoms during a six-month period, and social or occupational deterioration problems occur over a significant amount of time. These problems must not be attributable to another condition for the diagnosis of schizophrenia to be made.

By contrast, *schizophreniform disorder* is a short-term type of schizophrenia with the characteristic symptoms (including prodromal, active, and residual phases) being present for at least one month but not for the full six months required for the diagnosis of schizophrenia. In contrast to schizophrenia, the onset of schizophreniform disorder can be relatively rapid and the individual's level of functioning may or may not be affected. According to the American Psychiatric Association, about two-thirds of people with schizophreniform disorder do not recover and are subsequently diagnosed with schizophrenia.

Current Concepts and State of Knowledge

Historical Aspects

The clinical picture of schizophrenia was described for the first time by the German physician Emil Kraepelin who used the term "dementia praecox" to define a disorder with early beginning, a uniformly deteriorating course and a poor prognosis (Kraepelin ▸8). Subsequently, Eugen Bleuler coined the term "schizophrenia" and distinguished between fundamental and accessory symptoms of the disease (Bleuler ▸3, see Table ▸1). He believed that

the fundamental symptoms were present in all patients and were unique to the disorder while the accessory symptoms could also occur in other disorders. Bleuler realized that the condition was not a single disease and referred to a whole "group of schizophrenias". Some decades later, Kurt Schneider established the differentiation between first- and second-rank symptoms (Schneider ▸10, see Table ▸2), representing a preliminary stage of contemporary operationalized classification systems.

Table 1. Fundamental and accessory symptoms of schizophrenia (Bleuler ▸3).

Fundamental symptoms	Accessory symptoms
Loosening of associations	Hallucinations
Disturbances of affectivity	Delusions
Ambivalence	Catatonic symptoms
Autism	Speech abnormalities (e.g., mutism, neologisms)

Table 2. First-and second-rank symptoms (Schneider ▸10).

First-rank symptoms	Second-rank symptoms
Voices heard arguing	Other forms of hallucinations
Voices heard commenting on one's actions	Sudden delusional ideas
Audible thoughts	Perplexity
Thought insertion	Depressive or euphoric mood changes
Thought withdrawal	Emotional blunting
Thought diffusion	
Delusional perception	

In 1980, Timothy Crow postulated two dimensions of pathology underlying schizophrenia. According to his concept, the type I syndrome is mainly characterized by positive symptoms, potentially neuroleptic-responsive and reversible while the type II syndrome is mainly characterized by negative and cognitive symptoms, sometimes progressive and relatively irreversible (Crow ▸4, see Table ▸3).

Table 3. Two-syndrome concept of schizophrenia (Crow ▸4). (Reproduced with permission)

	Type I	Type II
Characteristic symptoms	Hallucinations, delusions, thought disorders (positive symptoms)	Affective flattening, poverty of speech, loss of drive (negative symptoms)
Type of illness in which most commonly seen	Acute schizophrenia	Chronic schizophrenia, the "defect" state
Response to neuroleptics	Good	Poor
Outcome	Reversible	? Irreversible
Intellectual impairment	Absent	Sometimes present
Postulated pathological process	Increased dopamine receptors	Cell loss and structural changes in the brain

The concepts described above have used a categorical approach, thereby indicating homogeneous, mutually exclusive subtypes of the disease. Essentially, schizophrenic disorders are heterogeneous and consequently, Peter Liddle has introduced a dimensional approach comprising three neuroanatomically classifiable syndrome clusters: psychomotor poverty, disorganization, and reality distortion (Liddle ▸9, see Table ▸4).

Table 4. Dimensional approach (Liddle ▸9).

Neuroanatomical dysfunction	Left dorsolateral prefrontal cortex	Medial temporal lobe	Right ventrolateral prefrontal cortex
Syndrome	Psychomotor poverty	Reality distortion	Disorganization
Symptoms	• Poverty of speech • Blunted affect • Slowness	• Delusions • Hallucinations	• Formal thought disorder • Distractibility • Incongruous affect

S

Psychopathology

Disorders of Thinking and Speech

Basically, thought processes may be disordered in form and content. Common formal thought disorders observed in schizophrenia patients include incoherent thinking. The patient's thoughts are illogical and confused up to a defect in processing and organizing language ("schizophasia"). During *thought block* thinking is decelerated and stagnant, and the patient's language is sagging accordingly. Thought content may be diminished as well. On the other hand, the term *flight of ideas* describes excursive and uncontrollable thinking, associations become loose and mental activity is generally accelerated. Furthermore, *improper responding to questions*, perseverations, paralogism, neologisms, and concretism are commonly observed in schizophrenia patients.

Essentially, content-disordered thought processes are equivalent to delusions. They are characterized by abnormal, apparently unreasonable interpretations of one's own experiences and perceptions to which the person concerned adheres despite refutation by others (▸Delusional disorder). According to Karl Jaspers, these interpretations fulfill three main criteria: certainty, incorrigibility, and impossibility (Jaspers ▸7). The most frequently observed delusions in schizophrenia patients are delusions of reference, of persecution and guilt as well as megalomania, nihilism, and delusions with religious content.

Many patients experience prepsychotic states and prodromal symptoms before the first episode of schizophrenia is apparent. For example, this stage of the illness includes attenuated psychotic symptoms (APS) or brief limited intermittent positive symptoms (BLIPS) (Prepsychotic states and prodromal symptoms).

Disorders of Affect and Mood

Schizophrenia is characterized by abnormalities of affect, emotional response, and mood. In this context, the profound disturbance of emotional rapport perceived in an intuitive way by an experienced psychiatrist interacting with a schizophrenia patient was named "praecox feeling". Due to fluctuations in attention and misinterpretation of stimuli, schizophrenia patients might be confused, depressed, and anxious. Sometimes, even situations of minimal novelty cause anxiety (novophobia), e.g., unfamiliar people, items, conversations. Common objects might take on undue significance and therefore scare patients. A further fundamental symptom of the schizophrenia-related affective disorder is parathymia, the inappropriateness of facial expression, gesture, and speech, which is contrary to the patient's real experience.

Affective flattening becomes manifest as a diminution of emotional response and indifference to events or topics that normally evoke such a response (Andreasen ▸2, see Table ▸5).

Table 5. Symptoms of affective flattening (Andreasen ▸2).

Unchanging facial expression
Decreased spontaneous movements
Paucity of expressive gestures
Poor eye contact
Affective nonresponsivity
Inappropriate affect
Lack of vocal inflections

Anhedonia refers to a pervasive and refractory reduction in the capacity to experience pleasure, which becomes apparent in reduced leisure activities or sexual interest.

Ambivalence is characterized by simultaneous, conflicting feelings toward a person or thing, e.g., love and hate or happiness and fear. These contradictory impulses are usually unconscious and uninterpretable for other people.

Depressive symptoms can be found in up to 50% of schizophrenia patients. On the other hand, some patients develop manic conditions characterized by hyperactivity, a reduced ability to think critically and an overestimation of their own capabilities.

Hallucinations

▸Hallucinations are conscious perceptions affecting the different senses in the absence of external stimuli. Auditory hallucinations are perceived as noise, words, sentences, whisper, or voices. They are apparent in about 70% of schizophrenia patients and mainly become manifest in thoughts becoming aloud as well as commenting, dialogic or imperative voices, respectively. Visual hallucinations occur relatively infrequently. Tactile hallucinations create the sensation of tactile sensory input and are perceived as touch, burning, or electrifying sensations. Coenesthesia is characterized by abnormal bodily sensations, e.g., parts of the body that are perceived as being changing their shape or size. Olfactory and gustatory hallucinations are quite uncommon in schizophrenia patients but can be associated with delusions of poisoning.

Disorders of the Ego

Patients with schizophrenia experience themselves in a disordered manner and often believe that they are affected by external forces. Accordingly, the

term "disorders of the ego" comprises various symptoms. For example, patients experiencing thought diffusion are convinced that other people know their thoughts. Other symptoms belonging to this category are thought withdrawal, thought insertion, depersonalization, and derealization.

Disorders of Psychomotor Functioning

Many patients with schizophrenia experience psychomotor disturbances already at an early stage of the illness. Accordingly, changes in facial expressions, gestures, posture, voice, and speech are often observed. Everyday activities have to be reconsidered (loss of automatisms), which is why patients appear mannered.

Catatonic phenomena comprise disorders of movement, speech, and autonomic function. These motor disturbances consist of hyper- or hypokinesias (excitement and inhibition, respectively) and parakinesias (abnormal postures, mannerisms, grimacing, stereotypies). Catatonic speech disorders include perseveration, echolalia, mutism, et cetera. Characteristic autonomic signs are dilatation of pupils, seborrhea, sweating, and alterations in muscle tone (rigidity or hypotonia, respectively). Catatonic stupor and excited states represent the extreme ends of the spectrum.

Cognitive Symptoms

▸Cognitive impairment is a cardinal feature of schizophrenia, which is found in 60–80% of patients. Generally, it is assumed that schizophrenia patients show deficits across a large number of neurocognitive domains including attention, executive functioning, memory, and fine motor skills. Performance has been reported to be two standard deviations below the mean of healthy control subjects. Cognitive variables have been related to the heterogeneity of functional outcomes, with difficulties in profiting from rehabilitation programs, and with quality of life. Evidence suggests that cognitive deficits may be of equal or greater importance in predicting functional outcome as positive or negative symptoms.

Such cognitive disturbances are present both in children who have a schizophrenic parent ("high risk children") and in first-degree relatives of patients, who do not suffer from a schizophrenic disorder. Furthermore, these deficits are apparent long before the onset of psychotic symptoms and they endure after a psychotic episode when patients are in remission. Therefore, cognitive deficits represent a possible trait marker of schizophrenia.

Next to neurocognitive impairment, schizophrenia has consistently been associated with deficits in the recognition, discrimination and experience of emotional stimuli. Impairments in affect perception have been demonstrated in chronic and first-episode patients and their unaffected siblings but not in high-risk individuals with initial prodromes, and it has been sug-

gested that the initial psychotic episode represents a critical point for the emergence of emotion perception deficits in schizophrenia spectrum illnesses. Several studies have shown that these deficits in emotion recognition are associated with illness-related measures such as duration of illness, symptomatology, symptom severity, and cognitive disturbances but are not influenced by age or antipsychotic treatment.

Other studies have shown significant and stable "theory of mind" (ToM) impairments in patients with schizophrenia. ToM refers to the ability to perceive other people's opinions, beliefs, and intents, and to establish a connection between these mental states and a person's behavior. These deficits are probably independent of neurocognitive dysfunctions and they might contribute to social and behavioral deviations in schizophrenia patients.

Subtypes

Depending on the combination of symptoms, different subtypes of schizophrenia have been defined:

Paranoid schizophrenia is characterized by relatively stable, often paranoid delusions, usually accompanied by (auditory) hallucinations and perceptual disturbances. Disturbances of affect, volition and speech, and catatonic symptoms are not prominent.

Hebephrenic schizophrenia is dominated by affective changes with shallow and inappropriate moods. Thought is disorganized leading to incoherent and rambling speech, whereas delusions and hallucinations are fragmentary if present at all.

Catatonic schizophrenia is mainly determined by psychomotor disturbances with alterations between extremes such as hyperkinesias and stupor.

Undifferentiated schizophrenia meets the diagnostic criteria for schizophrenia but does not conform to any of the above subtypes or exhibits the features of more than one of them without a clear predominance of a particular set of diagnostic characteristics.

The diagnosis of post-schizophrenic depression (▸Postpsychotic depressive disorder of schizophrenia) should be made if the patient has had a schizophrenic illness meeting the general criteria for schizophrenia within the past twelve months and some schizophrenic symptoms are still present. Depressive symptoms must be prominent and distressing, fulfilling at least the criteria for a depressive episode, and have been present for at least 2 weeks.

The term "residual schizophrenia" describes a chronic stage in the development of a schizophrenic disorder in which there has been a clear progression from an early stage (comprising one or more episodes with psychotic symptoms meeting the general criteria for schizophrenia described above) to a later stage characterized by long term, though not necessarily

irreversible, negative symptoms, i.e., psychomotor slowing, underactivity, blunting of affect, passivity and lack of initiative, poverty of quantity or content of speech, poor nonverbal communication by facial expression, eye contact, voice modulation, posture, poor self-care, and social performance. Simple schizophrenia represents an uncommon disorder characterized by a slowly progressive development of negative symptoms without any history of hallucinations, delusions, or other manifestations of an earlier psychotic episode, and with significant changes in personal behavior, manifest as a marked loss of interest, idleness, and social withdrawal.

Epidemiology, Risk Factors, and Course of Symptoms

The incidence of schizophrenia in industrialized countries ranges from 10–70 new cases/100,000, whereas prevalence rates range from 1.6 to 12.1/1,000. The lifetime risk is 0.5–1%. Both "social drift" and environmental risk factors (e.g., drug abuse, migration) might account for an increased prevalence in the lower socioeconomic classes.

Epidemiological studies have shown gender differences in the age of onset of schizophrenia. The peak age of onset is 10–28 years for men and 26–32 years for women. However, there is a second peak of onsets in women after the menopause, resulting in an equal lifetime incidence for both genders. Affected men make contact with the psychiatric services at an average of five years earlier than women do.

Both twin and adoption studies indicate genetic effects in the liability to schizophrenia. Although the mode of transmission has not been clarified, several studies corroborate the so-called multifactorial polygenic model that involves an interaction between many contributing genes and environmental factors (obstetric complications, prenatal infection, neurodevelopmental abnormality, substance misuse, social and psychological factors).

Approximately 20% of patients with schizophrenia improve without relapse and 40% achieve a clinically stable residual state and are socially integrated, whereas approximately one-third of patients suffer from continuous psychotic symptoms and/or increasing social disability. Factors affecting prognosis are listed in Table ▸6.

Table 6. Factors affecting prognosis.

Favorable prognosis	Unfavorable prognosis
Acute onset of illness	Insidious onset of illness
Positive symptoms	Negative symptoms
Lack of family history of schizophrenia	Family history of schizophrenia
Inconspicuous premorbid personality	Poor premorbid personality
Average IQ	Low IQ
High social class	Low social class
Social integration	Social isolation
Lack of comorbidities	Comorbid drug abuse
Female sex	Male sex
Being married	Single marital status

Treatment Considerations

The discovery of ▸chlorpromazine in the early 1950s introduced an era of effective pharmacological treatment for schizophrenia. Today, antipsychotics of different chemical structures, ranging from tricyclic ▸phenothiazines to thioxanthenes, ▸butyrophenones, dibenzazepines, substituted benzamides, benzioxazole derivatives, and chinolones are considered to form the backbone of treatment (▸Antipsychotic drugs, ▸First-generation antipsychotics, ▸Second-and third-generation antipsychotics, Future of antipsychotic medication). They shorten the length of an acute episode of the illness and reduce the risk of relapse. Clearly, modern concepts of schizophrenia management include psychosocial and rehabilitative measures, and pharmacotherapy should always be embedded in integrative treatment procedures.

Essentially, the prognosis of schizophrenia depends on when pharmacological treatment is started and on the number of psychotic episodes. Two-thirds of patients experiencing a first episode of the illness experience symptomatic remission within half a year if antipsychotic treatment is started immediately. In addition, consistent prophylaxis with antipsychotic medication results in a reduction of the one-year relapse rate from 75 to 20%. Since less than 50% of patients with schizophrenia in long-term treatment take their medication according to the physician's recommendations, interventions to enhance compliance should be implemented at the beginning of treatment (Fleischhacker et al. ▸6).

The parenteral administration of rapid-acting antipsychotics should be confined to emergencies, where acute agitation and lack of insight lead to a

high risk of patients harming themselves or others. In contrast, the administration of long acting depot antipsychotics is an important treatment option for the long-term management. The advantages of these injectable drugs include dose reduction due to avoidance of the first-pass-effect, the fact that patients do not need to take medication every day, and the facilitation of management due to certainty concerning compliance. The disadvantages of this type of treatment include the fact that some patients refuse intramuscular injections or develop irritations at the injection site. Another problem is that the dose of a depot antipsychotic cannot be reduced once administered.

Despite continuous new findings in the field of psychopharmacology, there are no reliable predictors for individual drug response/tolerability. Therefore, the choice of medication depends on an individual risk–benefit analysis. In patients who do not adequately respond to two antipsychotic drugs of different chemical classes, switching to ▸clozapine is indicated. This compound has been shown to have unique efficacy in so far as it reduces symptoms in 30–60% of treatment refractory schizophrenia patients (Fleischhacker ▸5) (▸Antipsychotic drugs). However, although pharmacological agents have substantially advanced the treatment of schizophrenia and have had a significant impact on the lives of patients in terms of relapse prevention, quality of life, and resocialization there are still considerable unmet needs in the management of these patients.

Cross-References

▸Delusional Disorder
▸First-Generation Antipsychotics
▸Hallucinations
▸Postpsychotic Depressive Disorder of Schizophrenia
▸Second and Third Generation Antipsychotics

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Schizophrenia Prodrome

Definition

Subthreshold psychotic symptoms that emerge prior to meeting full criteria for schizophrenia (or before relapse after remission of symptomatology).

Cross-References

▸Pre-psychotic States and Prodromal Symptoms
▸Schizophrenia

Second and Third Generation Antipsychotics

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Synonyms

Atypical antipsychotics
Novel antipsychotics

Definition

This class of antipsychotics, with clozapine as the prototype, are distinguishable from their first generation counterparts by a lower liability for extrapyramidal symptoms (EPS) and claims of improved efficacy that extend to other domains beyond psychosis (e.g., cognition, negative symptoms). These drugs have been designated "atypical" when compared to the

older "typical" or conventional antipsychotics like ▸chlorpromazine, ▸haloperidol, ▸perphenazine and fluphenazine.

The distinction between second and third generation antipsychotics has been made based on mechanistic differences. Specifically, aripirpazole is the first approved antipsychotic that is a partial ▸dopamine agonist and, as such, has been designated a third generation antipsychotic. This presumes that all other atypical compounds to this point, including clozapine, share some common attribute(s) pharmacologically that account for their unique clinical profile. However, beyond dopamine D2 antagonism, which characterizes all antipsychotics including ▸aripiprazole, this is not the case. For example, the serotonin 5-HT2 /dopamine D2 model does not adequately represent all of these compounds (see *Atypicality: Mechanisms of Action*, below). Thus, as a partial dopamine agonist aripiprazole is unique amongst the atypical antipsychotics but the distinction between second and third generation agents may misrepresent the homogeneity of all other atypicals.

Pharmacological Properties

First Generation Antipsychotics and Limitations

Antipsychotics were introduced for clinical use in the 1950s. At the time, descriptive terminology included "major tranquilizers" (because of their sedating/calming effect) and "neuroleptics", literally meaning "to take the neuron" and reflective of their liability for motor side effects (i.e., EPS). They rapidly became the treatment of choice for psychotic conditions such as schizophrenia although it was initially unclear as to what aspect of their diverse pharmacology accounted for this effect. Within the next years, it was established that dopamine D2 binding seemed critical to the antipsychotic effect and this generated an additional subgroup of these drugs characterized by high affinity for the dopamine D2 receptor, drawing a distinction between low-potency (e.g., chlorpromazine) and high-potency (e.g., haloperidol) neuroleptics. A liability for EPS, both acute (e.g., parkinsonism) and chronic (e.g. ▸tardive dyskinesia or TD) characterized all these drugs and represented a substantial burden to their use in the clinical setting.

Clozapine

Clozapine, developed in the 1960s, was notable for its antipsychotic efficacy in the face of minimal EPS at therapeutic doses. It was introduced for clinical use in the early 1970s but soon withdrawn in a number of countries because of a cluster of deaths, subsequently linked to its associated risk of agranulocytosis. Work in the late 1980s, though, underscored this drug's superiority in treatment resistant schizophrenia and suggested it might also have broader efficacy (i.e., negative as well as positive symptom improvement).

By the 1990s it was reintroduced in different countries with the associated requirement of regular hematologic monitoring.

Atypicality

Atypicality has been defined as lack of EPS at therapeutic doses (Meltzer et al. ▸6). At the time of clozapine's development, it was unique amongst existing antipsychotics in this regard, establishing it as the prototype of atypicality. Over time, a new class of antipsychotics (second generation) was developed to mirror clozapine's clinical benefits while circumventing its adverse side effects, in particular risk of agranulocytosis. In this process, it was assumed that these drugs would also mirror clozapine in other regards (e.g., greater efficacy in treatment resistant schizophrenia, improvement in negative as well as positive symptoms). With a new class of antipsychotic available, the previous medications came to be designated "first generation" (vs. second generation), "typical" (vs. atypical) or "conventional" (vs. novel).

Atypicality: Mechanisms of Action

Several aspects of clozapine's diverse pharmacology were highlighted as possibly contributing to its unique clinical profile. These included its low binding affinity for the dopamine D2 receptor in addition to comparatively high binding at the serotonin 5-HT2 receptor. An elegant body of pre-clinical work led Meltzer et al. to postulate that the profile of greater serotonin 5-HT2 versus dopamine D2 binding accounted for clozapine's atypical features (Meltzer et al. ▸6), a model that was rapidly embraced in drug development and one that describes most second generation antipsychotics including ▸olanzapine, paliperdione, ▸quetiapine, ▸risperidone, sertindole, ▸ziprasidone and zotepine. Critical to this model is the ratio of serotonin 5-HT2 versus dopamine D2 binding; earlier antipsychotics demonstrated combined serotonin 5-HT2/dopamine D2 antagonism but did not meet this identified ratio and were not seen as unique clinically.

Clozapine's low affinity for the dopamine D2 receptor also called into question the longstanding argument that dopamine D *2* antagonism is absolutely critical for antipsychotic efficacy. This encouraged efforts to look at non-dopaminergic strategies and, following the importance this model ascribed to serotonin, led to work investigating the notion that serotonin 5-HT2 antagonism alone might be sufficient (e.g., ritanserin, MDL-100907, fananserin). While this was not substantiated, there continues to be interest in the pursuit of antipsychotic development that is not hinged on dopamine blockade.

Although the serotonin 5-HT2/dopamine D2 model was widely embraced, there was reason to pursue other explanatory models. In countries outside

of North America, ▸amisulpride and ▸sulpiride (substituted benzamides) are accessible clinically and seen as atypical; however, their pharmacological profile precludes an explanation based on serotonin 5-HT2/dopamine D2 antagonism. At least two other models have since been posited to account for the atypical features of newer antipsychotics. The "low affinity-fast dissociation" model (Kapur and Seeman ▸4) holds that clinical benefits such as decreased EPS, lack of prolactin elevation, and possible improvement in cognitive and negative symptoms may occur as a result of transient binding at the dopamine D2 receptor, which mitigates against impairment of phasic dopamine release. Thus, while all drugs depress tonic dopamine release, those with more rapid dissociation (i.e., fast Koff drugs) are less likely to alter phasic dopamine release, essential for dopamine to exert its physiologic effects in the course of daily activities. There is, for example, abundant evidence linking dopamine to reward and goal-directed behaviors, as well as cognition (Berridge ▸1). This line of thinking suggests there may be clinical gains through what these drugs *don't do* (i.e., sustained dopamine blockade) rather than by unique gains attributable to some other aspect of their rich receptor-binding profiles (e.g., concomitant serotonin 5-HT2 binding).

A second hypothesis ascribes the clinical gains associated with atypicality to limbic selectivity (Bischoff ▸2) and support for this comes from several lines of investigation (Remington and Kapur ▸8). Looking at early gene expression (c-fos and c-jun) as a marker of synaptic activity, it has been noted that as a class the newer antipsychotics are associated with regional differences (e.g., increased c-fos expression in limbic versus striatal regions). Similarly, more recent opportunities to examine D2 binding extrastriatally have provided evidence that atypical antipsychotics demonstrate preferential binding for extrastriatal structures, for example temporal cortex. This could account for the diminished risk of EPS and hyperprolactinemia, as well as a more direct effect on other brain regions. Of note, while the atypicals as a class are associated with decreased EPS and a diminished risk of hyperprolactinemia, this is variable; risperidone, paliperidone, and the substituted benzamides carry a greater liability. It has been suggested that the limbic selectivity model is, at least in part, a variation of the low affinity-fast dissociation hypothesis in that the decreased binding in striatal regions reflects competitive displacement by endogenous dopamine at dopamine D2 receptors in dopamine-rich regions.

The distinction between aripiprazole and other atypical antipsychotics is, in contrast, clearer and draws upon a shift in thinking regarding dopamine's role in schizophrenia. For decades, the most widely held biochemical model for schizophrenia posited a disorder of hyperdopaminergic activity. However, by the 1980s a clearer distinction was drawn between positive and

negative symptoms, and subsequently our conceptualization of schizophrenia has broadened even further to include other domains (e.g., cognition). In the context of these changes, dopamine's role has been reframed to accommodate its differential involvement in this expanded model, suggesting more complex feedback loops involving various dopamine receptors and other neurochemical systems. For example, while limbic structures, dopamine D2/D3 receptors, and hyperdopaminergic activity have been implicated in the positive symptoms, cognitive and negative symptoms have been linked to prefrontal regions, a role for dopamine D1 receptors, and hypodopaminergia.

In this context, drugs that affect dopamine differentially may have distinct clinical advantages and aripiprazole's proposed dual action on dopamine fits with this line of thinking. A partial dopamine agonist acting on postsynaptic D2 receptors as well as presynaptic dopamine autoreceptors, its effects are linked to whether dopamine activity is high (i.e., mesolimbic) or low (i.e., mesocortical). Thus, through its antagonist properties it diminishes positive symptoms (mesolimbic), while its agonist profile results in improved negative and cognitive symptoms (directly at the mesocortical level and indirectly at the nigrostriatal level in the form of attenuated EPS). The popularity of each of these models speaks to the importance of dopamine and serotonin in explaining the unique clinical benefits of the newer antipsychotics, but these drugs are characterized by diverse pharmacological profiles that impact a variety of receptors and systems (e.g., acetylcholine, norepinephrine, histamine, glutamate) (Remington and Kapur ▸8). Although the currently available newer antipsychotics can each be characterized by one of the aforementioned models, the potential role(s) of these other systems remains a subject of investigation, both in terms of therapeutic efficacy as well as side effects. The involvement of other receptors and systems has taken on added interest with the growing body of evidence conceptualizing schizophrenia as a disorder of multiple symptom domains (e.g., positive, negative, cognitive, affective), paralleled by increased awareness regarding the clinical and functional importance of these other nonpsychotic features. The potential benefits of an effective antipsychotic without direct dopamine blockade remains alluring, ensuring the search for new antipsychotics focused on other systems thought to play an important role in schizophrenia.

Atypicality: Second/Third Generation Antipsychotics

While Meltzer et al. defined atypicality as absence of notable EPS at therapeutic doses (Meltzer et al. ▸6), evidence clearly indicates that the newer antipsychotics are not the same in this regard. For example, risperidone has been identified as having a greater liability for EPS than many other atypical

agents, a risk that is dose-dependent – this also distinguishes it from other atypicals such as clozapine and quetiapine. It must also be noted that the benefits of the atypical antipsychotics, particularly agents like risperidone, in terms of EPS have been challenged on methodological grounds; often comparator trials with first generation antipsychotics have used haloperidol, which has a notable propensity for EPS, and at doses in excess of what are currently recommended. It remains, though, that as a class the atypicals have been associated with diminished risk of EPS and it is this defining feature that best distinguishes atypical antipsychotics from their conventional counterparts.

Although classifying medications based on presence or absence of a particular side effect may seem misguided, it has occurred again more recently with the growing recognition that the newer antipsychotics, in particular agents like clozapine and olanzapine, demonstrate a substantially greater risk for weight gain and associated metabolic disturbances. At least some regulatory bodies have chosen to identify this as a class effect characterizing all atypicals although evidence clearly indicates that, as with EPS, there are marked differences between these drugs on this dimension. For example, at the other end of the continuum from olanzapine and clozapine are drugs like ziprasidone and aripirazole that are considered to be "weight neutral" (Newcomer ▸7).

Other definitions, for example based on mechanism(s) of action, are even less homogeneous. While the serotonin 5-HT2/dopamine D2 hypothesis dominated initial efforts to replicate clozapine's clinical advantages, agents now classified as atypical cannot be collectively grouped within this model. Clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine can be categorized as serotonin 5-HT2/dopamine D2 antagonists but this is not the case for amisulpride and sulpiride, where their benefits might best be explained by the low affinity-fast dissociation model. In fact, it has been argued that this same model could as readily explain the benefits of drugs that meet criteria for serotonin 5-HT2/dopamine D2 antagonists although this is the subject of ongoing debate. As a partial dopamine agonist, aripiprazole currently stands alone pharmacologically, which has led some to suggest that it represents a third generation antipsychotic. This is, of course, a misnomer if we are to use serotonin 5-HT2/dopamine D2 antagonism as the mechanism of action that categorizes all other newer antipsychotics (given the substituted benzamides). The low affinity-fast dissociation explanation might better capture other antipsychotics, but this debate itself speaks to the pitfall of classifying such diverse pharmacological agents on models that are hypothetical and singularly focused. It is very likely that the clinical gains we are seeking to achieve can

be attained through different pathways, and that benefits may be accrued through a combination of pharmacological manipulations.

Attempting to collectively group these agents based on clinical similarities faces similar challenges, (Tandon et al. ▸9), made more difficult by the rapid expansion in purported benefits that occurred in parallel to the development of the different atypicals.

The fact that the atypical antipsychotics differ on various measures of efficacy and side effects, in combination with evidence that clinical differences between them and first generation antipsychotics may not be as prominent as once thought, has challenged the utility of terminology like "second generation" (Leucht et al. ▸5). As an alternative, it has been argued that this "all or none" approach to categorization should give way to a strategy that allows individual drugs to be defined across a number of relevant measures (i.e., different clinical measures and side effects) (Waddington and O'Callaghan ▸10).

Formulations

All atypical antipsychotics are available in oral preparations that call for once daily administration. There are examples where it is recommended that the dose be twice daily, based on shorter elimination half-life (e.g., quetiapine, ziprasidone), although extended-release oral formulations have been developed to address this (e.g., quetiapine). There is some question as to the value of establishing daily dosaging based on peripheral pharmacokinetics, as in vivo neuroimaging techniques such as positron emission tomography (PET) have demonstrated that central kinetics do not necessarily mirror what is observed peripherally.

With certain atypical antipsychotics, variations in formulations have been marketed to ease administration and adherence. These include rapidly dissolving, oral formulations (e.g., risperidone, olanzapine), short-acting intramuscular for acute treatment (e.g., risperidone, olanzapine, ziprasidone), and longer-acting depot formulations for maintenance treatment (e.g., risperidone, administered every 2 weeks). At least some of the first generation antipsychotics had also developed shorter and longer acting injectable formulations, but the rapidly dissolving oral formulation is unique to the newer medications.

Pharmacokinetics

(see Antipsychotics)

Efficacy and Effectiveness

Central to antipsychotic development was the goal of more tolerable agents from the standpoint of EPS, but limitations in the efficacy of first generation

antipsychotics also represented an impetus. As many as 25–30% of individuals treated with these drugs were designated treatment-resistant or refractory, with an additional subgroup deemed only partially responsive. Furthermore, these drugs, while at least reasonably effective in treating positive symptoms (e.g., delusions, ▸hallucinations), were not particularly useful in controlling negative symptoms (e.g., amotivation, alogia).

With clozapine there was evidence that it was superior to first generation antipsychotics on both these domains, in addition to its improved EPS profile. Thus, implicit in the development of other antipsychotics that were intended to mirror clozapine was the assumption of similar clinical benefits. As the list of new agents expanded so too did the purported benefits though, with suggestions that these drugs demonstrated clinical superiority on other symptoms (e.g., cognitive, affective) and outcome measures (e.g., quality-of-life, adherence).

Initial efficacy trials generally demonstrated superiority of the different atypical agents versus a first generation antipsychotic on total clinical (e.g., Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS)) and positive symptoms scores, and frequently negative symptom scores as well. However, many of these efficacy studies were subsequently challenged methodologically; not only were the trials relatively short (i.e., 6–8 weeks), they often employed haloperidol as the comparator, a typical antipsychotic with notable propensity for EPS, at doses in excess of what are currently recommended.

Similarly, questions arose over claims of superior efficacy in other symptom domains. These followed two lines of thinking: (a) the magnitude of change and extent of difference between the atypical agents and first generation antipsychotics; and (b) factors underlying such changes. With regard to the former, claims regarding the extent of improvement on neuropsychological measures were tempered over time, with current thinking that at best these changes are modest and not of a magnitude that would translate to notable differences in ▸functional outcome. For negative symptoms as well, subsequent evidence fostered a rethinking of how much different atypical antipsychotics were. In both cases, initial claims implicated unique aspects of these new drugs and their pharmacology (e.g., greater serotonin 5-HT2 antagonism). However, an alternative explanation suggested that methodological issues, discussed earlier, favoring the atypicals could account for much of these differences. Further, the possibility was raised that gains could be explained, at least in part, not by what these drugs did through different receptors and systems compared to first generation antipsychotics, but by what they didn't do (i.e., invoke high and sustained levels of dopamine D2 binding). Evidence demonstrated that this was associated with various ad-

verse effects beyond motor and endocrine problems (EPS and hyperprolactinemia), including dysphoria, amotivation, and cognitive impairment. More recently, the research focus shifted from an assessment of atypical antipsychotics in the context of smaller and circumscribed efficacy trials to larger effectiveness studies thought to be more representative of "real world" clinical practice. Once again, results have suggested that differences between atypicals and first generation antipsychotics are notably smaller than once thought. They have also provided further evidence that clozapine is clinically superior, even amongst other atypicals, in treating treatment resistant schizophrenia. Of note, there is some suggestion that amongst other atypical antipsychotics there may be clinical differences, a position that has been supported through other larger scale approaches such as meta-analytic studies. As of yet, such differences are not well established, with methodological issues (e.g., dosing) making conclusions of this sort difficult (Leucht et al. ▸5; Tandon et al. ▸9).

Treatment Algorithms

Current guidelines advocate atypical antipsychotics as first-line treatment for schizophrenia and related psychotic conditions. There is a lack of evidence that these drugs are more effective in this population, although decreased liability for EPS, including TD, and hyperprolactinemia, in combination with improved tolerability represent advantages from the standpoint of side effects. However, the increased risk of weight gain and metabolic disturbances that can be observed with at least some of the atypicals, in conjunction with their higher cost and lack of clear clinical superiority, have more recently challenged this position.

Clozapine is generally advocated as treatment of choice following suboptimal response to two antipsychotic trials. This is in line with evidence that it is superior to all other antipsychotics in the treatment resistant population, and that treatment resistance can be seen quite soon after the illness' onset. There is no consistent evidence that combinations of antipsychotics, including those that include clozapine, offer superior clinical efficacy in individuals who have not responded to monotherapy (i.e., one antipsychotic).

Paralleling the increased number of atypical antipsychotics has been a rise in off-label use of these medications and efforts to expand their indications. Their efficacy in a variety of psychiatric disorders is being examined (e.g., pervasive developmental disorder; generalized anxiety disorder; psychotic depression), and as a result their approved indications has grown (e.g., autism; bipolar disorder, manic and mixed states), depending on agent and regulatory body.

Side Effects

As a class, the atypical antipsychotics continue to be seen as better from the standpoint of EPS, although such a distinction is less clear depending on a variety of factors that include specific agent, comparator first generation antipsychotic, and dose. Current evidence, albeit limited, does favor the atypicals as well in terms of TD risk (Correll and Schenk ▸3), a significant clinical advantage should this finding hold true. There is also an indication that as a class the atypical antipsychotics might be better tolerated. While there was an expectation that such benefits would translate to improved adherence, this has not been confirmed, a reminder that non-adherence is complex and multi-factorial.

Atypical antipsychotics, to varying degrees, also share side effects that were identified with their first generation counterparts (e.g., sedation, postural hypotension). In general, the atypicals have a lower risk of hyperprolactinemia, although this is variable; risperidone, paliperidone, and the substituted benzamides carry a greater liability. There was anticipation that neuroleptic malignant syndrome (NMS), a potentially fatal adverse event that can occur with all first generation antipsychotics, would be diminished or even absent with the atypical agents; however, all of the newer drugs to date, including clozapine, appear to carry this risk and it is not yet clear as to whether the overall liability has been reduced.

Although the atypical antipsychotics appear superior from the standpoint of movement disorders, concern has been raised about their increased liability for weight gain and associated metabolic disturbances, including dyslipidemia and type 2 diabetes. This, in turn, translates to a greater risk of metabolic syndrome, cardiovascular risk and associated mortality. There is added concern because schizophrenia has already been associated with a shortened lifespan (independent of suicide) which may be related to various factors (e.g., economic, lifestyle, access to medical care). Moreover, there is some evidence to suggest that schizophrenia itself may be a risk factor for diabetes. As with EPS, the atypicals vary in risk of weight gain, with olanzapine and clozapine identified as carrying the greatest risk, while at the other end of the spectrum aripiprazole and ziprasidone have been identified as "weight neutral" (Newcomer ▸7).

In the geriatric population, atypical antipsychotics have been associated with increased risk of death (in the range of 1.6 fold) from varied causes (e.g., cardiovascular, infectious). In fact, though, both typical and atypical antipsychotics have been linked to increased mortality rates in schizophrenia (Weinmann et al. ▸11). Data regarding safety and efficacy in the pediatric population are limited.

Conclusions

With clozapine as the prototype, a number of new antipsychotics have been developed. Collectively, they have been termed "atypical" and further distinguished as "second" or "third generation" antipsychotics. Atypical differentiates these drugs from their conventional counterparts based on clinical profile, specifically diminished risk of EPS, although this definition subsequently broadened to include a variety of other measures. The distinction between second and third generation antipsychotics is mechanistic, with aripiprazole (third generation) the only atypical antipsychotic to date that is a partial dopamine agonist.

The difference between these newer drugs and so-called typical antipsychotics may not be as notable as once thought, with the exception of clozapine's clinical superiority to all other antipsychotics in treatment resistant schizophrenia. Further, "atypical antipsychotics" implies a homogeneity amongst these newer drugs and separation from first generation antipsychotics that may be both misleading and confusing. There are differences between atypicals on a variety of clinical/biological measures, and even the distinction between second and third generation antipsychotics implies two distinct mechanisms of action. However, this belies the complexity of pharmacological features that may underlie clinical differences.

This said, the atypical antipsychotics represent a clinical advance and the first notable shift in schizophrenia's pharmacotherapy since chlorpromazine. Moreover, they have stimulated numerous lines of research that have substantially impacted our understanding and conceptualization of schizophrenia. The clear limitations of these medications as well in terms of clinical response and side effects, though, underscore the need for better drugs. The widespread claims of atypical antipsychotics were in keeping with a "magic bullet" approach, where a single drug could be effective across the multiple symptom domains now defining schizophrenia. However, it may well be that a multi-dimensional approach, premised on the notion that each domain reflects different pathophysiologic mechanisms, proves a more useful strategy.

Cross-References

- ▸Atypical Antipsychotic Drugs
- ▸CATIE
- ▸EUFEST
- ▸Extrapyramidal Motor Side Effects
- ▸Functional Outcome

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Striatum

Synonyms

Neostriatum

Definition

The striatum is a subcortical brain structure. The *corpus striatum*, which includes the putamen rostrally and the caudate nucleus caudally, is a com-

ponent of the ventral cerebral hemisphere, receiving strong projections from the cerebral cortex and projecting back to it via the thalamus. In addition, the striatum receives a robust dopaminergic innervation from the *substantia nigra* and the ventral tegmental area. It is fundamental for the selection of motor programs in response to external signals, which is triggered by dopaminergic signaling. Its ventral component, the ventral striatum or nucleus accumbens, is a key element in the response to salient stimuli predicting reward, hence inducing intensely motivated states.

Sulpiride

Definition

Sulpiride is a typical antipsychotic based on antagonism of postsynaptic D2 dopamine receptors. Agonism at the gamma-hydroxybutyrate receptor may contribute to its antipsychotic properties. Sulpiride has fewer extrapyramidal side effects, but also reduced antipsychotic potency, as compared with many other typical antipsychotics. At lower doses than used for antipsychotic treatment, its prominent action is presynaptic dopamine autoreceptor antagonism, giving rise to antidepressant and stimulating effects. Secondary clinical uses are thus treatment of depression and vertigo. Sulpiride is currently not approved in the USA and Canada. Together with the atypical antipsychotic sultopride, sulpiride falls under the chemical class of benzamides.

Cross-References

▸First-Generation Antipsychotics

Tardive Dyskinesia

Definition

Tardive dyskinesia (TD) is a chronic neuromotor side effect of dopamine-blocking medications, characterized by abnormal involuntary movements of voluntary musculature that are generally slow and that can be irreversible. It can include abnormal rotatory or sinuous movements of the mouth, lips, neck, trunk, hands, arms, and legs. It is identified as a side effect of long-term antipsychotic use; risk factors have been identified (e.g., age, duration of exposure), but there is no specific means of precisely predicting who will develop TD. With the ▸first-generation antipsychotics, prevalence rates in chronically treated patients approximated to 25%. Evidence for the newer, "atypical" antipsychotics indicates that none of these agents are without risk of TD, although prevalence rates appear notably lower. The precise pathophysiologic mechanisms underlying TD have not been elucidated, although high and sustained levels of dopamine D2 occupancy have been implicated. Many putative pharmacologic treatments have been investigated, although only a few (e.g., tetrabenazine in Canada) have gained an indication for treatment of TD. TD has proven inconsistent in its response to all treatments, variable over the course of the illness, and is frequently irreversible. Other tardive movements (e.g., tardive dystonia) are also linked to chronic antipsychotic exposure.

Cross-References

▸First-Generation Antipsychotics
▸Schizophrenia
▸Second-Generation Antipsychotics

Thioridazine

Definition

Thioridazine, like other compounds of its chemical class (▸phenothiazines), is classified as a typical antipsychotic, although its pharmacological profile exceeds dopamine D2 receptor blockade to include antagonism at dopamine D1, alpha-1 adrenergic, and muscarinic cholinergic receptors, and it produces a relatively low incidence of extrapyramidal side effects. Cardiotoxicity, retinopathy, and other serious side effects have reduced its use to patients who do not respond to other commonly used antipsychotic compounds.

Cross-References
▸First-Generation Antipsychotics

Thiothixene

Definition
Thiothixene acts at multiple receptors but mainly by dopamine D2 blockade. It is a first generation antipsychotic with an elimination half-life of 34 h, and is mainly metabolized by 1A2 CYP450 isoenzymes.

Cross-References
▸First-Generation Antipsychotics

Thioxanthenes

Definition
A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in treatment of schizophrenia. Among the widely used drugs in this category are chlorprothixene, ▸flupenthixol, and zuclopenthixol.

Cross-References
▸First-Generation Antipsychotics

Treatment-Resistant Schizophrenia

Synonyms
Refractory schizophrenia

Definition
Schizophrenia is considered as a heterogeneous illness with various trajectories of response and treatment outcome. A minority of individuals demonstrate complete resolution of symptoms; at the other end of the spectrum, approximately 25–30% of individuals show minimal response to treatment, at least with ▸first-generation antipsychotics. It is these individuals who are designated as refractory or treatment resistant and there are now established criteria to make this diagnosis, criteria that take into consideration previous treatments (including drug, dose, and duration) as well as outcome.

It is important to distinguish this subpopulation of individuals from "partial responders". This latter group also manifests a suboptimal response, but it is more substantial than what is observed in the treatment-resistant population.
The distinction of treatment resistant has important clinical implications, as ▸clozapine appears superior to all antipsychotics, including other atypicals, in treating this population. It is estimated that a significant response will be seen in approximately 30–50% of clozapine-treated individuals.
Treatment-resistant schizophrenia can be seen from the earliest stages of schizophrenia, although it can also be observed in individuals who initially appeared responsive to treatment. There are no well-established criteria that can be used clinically to predict which individuals will be refractory or responsive to clozapine.

Tremor

Definition

Mostly rhythmic muscular contractions and relaxation of different parts of the body, for example, hands and fingers. Can be part of various, mostly neurological, disorders or induced by medications such as antipsychotics.

Trifluoperazine

Definition

Trifluoperazine acts at multiple receptors but mainly as an antagonist at dopamine D2 receptors. It is a phenothiazine, a first-generation antipsychotic with a plasma half-life of around 13 h. The active 7-hydroxymetabolite has a half-life of 10 h.

Cross-References

▸First-Generation Antipsychotics

Trihexyphenidyl

Definition

Trihexyphenidyl is an anticholinergic agent that binds to M1 muscarinic receptors. It blocks the parasympathetic nervous system and causes relaxation of smooth muscle. It is indicated for the treatment of Parkinsonism

and drug-induced extrapyramidal symptoms. Toxicity and side effect symptoms resemble that of atropine.

Typical Antipsychotics

Synonyms

Classical neuroleptics
Conventional antipsychotics
▸First-generation antipsychotics

Definition

Typical antipsychotics are a class of antipsychotic drugs first developed in the 1950s to treat schizophrenia. Typical antipsychotics may also be used for the treatment of acute mania, agitation, and other conditions.

Ventral Tegmental Area

Synonyms
VTA

Definition
The ventral region of the midbrain, where ▸dopamine (DA) cell bodies that project to limbic structures and cortical areas are located.

Ventromedial Prefrontal Cortex

Definition
Ventromedial prefrontal cortex is a part of the ventral part of the brain that plays a role in decision-making and the processing of fear and risk-taking.

Ziprasidone

Definition

Ziprasidone is a 2nd generation antipsychotic with antagonistic properties at serotonin, dopamine and histamine receptors. It also blocks the reuptake of noradrenaline and serotonin. Among the 2nd generation antipsychotics it has, together with aripiprazole, the least propensity to induce metabolic side effects.

Cross-References

▸Second- and third-generation antipsychotics