Encyclopedia of Schizophrenia

Focus on Management Options

W. Wolfgang Fleischhacker
Ian P. Stolerman
Editors

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Ian P. Stolerman (Eds.)

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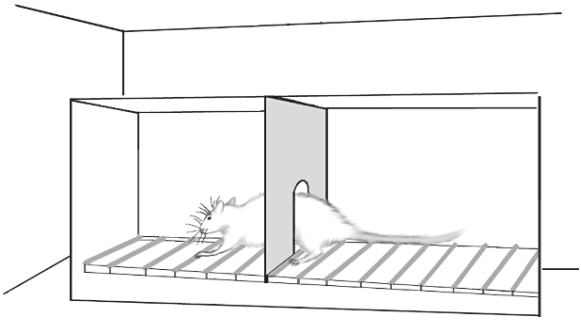
chologist B.F. Skinner. Skinner showed that a certain behavior could be maintained by the consequences it produced, and called this type of behavior operant behavior (Operant behavior in animals). Thus, operant behavior (such as active avoidance response) can be defined as behavior that is maintained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

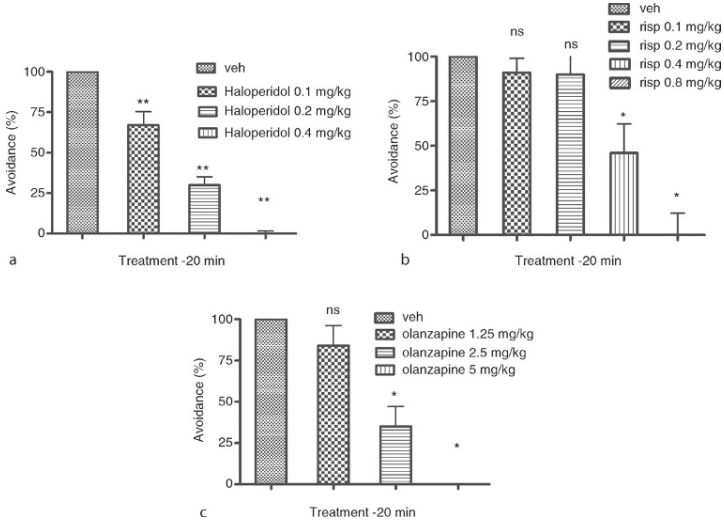
potential antipsychotic activity of new drugs tested with high predictive certainty. The active avoidance test has also been shown to have some construct validity (i.e., selective suppression of avoidance may mimic a blockade of some pathophysiological mechanisms in schizophrenia). Thus, the local application 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-