Neurologic Side Effects of Psychiatric Treatments

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Little is known in psychiatry concerning fundamental disease processes. The relative absence of disease-specific treatments is therefore not surprising. Most physical treatments in psychiatry exert their therapeutic effects in a nonspecific fashion. Lack of disease specificity means that compromises are continually made between beneficial and unwanted treatment effects. Indeed, the goal of most therapeutic developments, given limitations in knowledge concerning disease processes, is to enhance wanted over unwanted effects.

Physical treatments in psychiatry, as in other branches of medicine, aim to ameliorate, arrest, and reverse disease processes. In practice, the arrest or reversal of psychiatric disease is an idealistic and rarely achieved goal. In this, psychiatry shares much in common with neurology in that symptom relief is the principal therapeutic aim.

Despite these limitations, there are many beneficial and effective treatments in psychiatry. The mediation of these effects is generally ascribed to alterations in neuronal function at neuroreceptor sites. However, a lack of pharmacologic and disease specificity means that psychiatric interventions are associated with high rates of unwanted effects. Because of their high prevalence, neurologic side effects are the most important hazards of psychiatric treatments. The recognition of neurologic side effects is therefore of great clinical importance.

This review examines the prevalence, clinical presentation, putative pathophysiology, and management of neurologic side effects of psychiatric treatments. It is not possible within the brief space of this article to cover all treatments in psychiatry; therefore the focus will be on the more conventional and widespread treatments. These include the neuroleptics, lithium, antidepressants, electroconvulsive therapy (ECT), anxiolytics, and psychosurgery.

NEUROLEPTICS

This broad group of compounds constitutes the cornerstone of pharmacologic treatment of the psychoses, particularly schizophrenia. The introduction of potent antipsychotic agents into clinical practice in 1952 was associated with an almost immediate recognition that these agents could result in neurologic side effects. Side effects may for convenience be thought of as acute and chronic, though in reality such a division is arbitrary and artificial. There is little dispute that neuroleptics cause acute neurologic side effects, but there is controversy as to whether they are either necessary or sufficient causes for the emergence of chronic side effects, in particular tardive dyskinesia (TD).

This question will be addressed further in considering TD. The most commonly encountered neurologic side effects of neuroleptics are summarized in Table 1.

ACUTE DYSTONIC REACTIONS

Acute dystonic reactions were first reported in association with chlorpromazine treatment. Because of their distribution, they were labeled “facio-bucco-linguo-masticatory dyskinesia” and the similarity with “excito-motor” syndromes seen in the wake of epidemic encephalitis was noted. These reactions may be focal or generalized. Their onset, which is abrupt, is associated with com-

Table 1. Neurologic Side Effects of Neuroleptics

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<th>Neuroleptic side effects of psychiatric treatments</th>
<th>Neuroleptic malignant syndrome</th>
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<td>Akathisia</td>
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The pathophysiology of drug-induced akathisia is continuous, stereotyped, and repetitive. Surprisingly, the condition is frequently mistaken to a tic, though akathisia differs in that the urge to move is constant and the motor component lies the inner subjective urge to move and not sitting, or constant pacing. Motor activity results in agitation. The association of an inner urge and rocking back and forth, crossing and uncrossing the legs, or constant pacing, may lead to bizarre gait or difficulties in walking.

Acute dystonic effects are usually seen in the first 72 hours of neuroleptic treatment. They affect up to 5% of all patients started on these compounds. The pathophysiology of acute dystonic reactions is unknown, though the clinical manifestations suggest an excess dopaminergic activity, possibly secondary to acute antagonism of dopamine autoreceptors. Acute dystonic reactions are most prevalent in young male patients. They can occur with any type of neuroleptic but are seen most often in association with the piperazine side chain phenothiazines and the butyrophenones. They are reversible either spontaneously or with treatment. An episode can usually be terminated abruptly by injection of an antiparkinsonian drug. Treatment with neuroleptics can, however, be continued with only a slight risk of recurrence.

**AKATHISIA**

This refers to a condition characterized by a subjective sense, frequently accompanied by objective evidence, of restlessness. Although reported in postencephalitic and idiopathic parkinsonism, it is now most frequently encountered in patients on neuroleptic drugs. The condition usually presents in the first month of neuroleptic treatment. A delayed-onset variant, tardive akathisia, is reported in up to 25% of patients with TD.

Patients with akathisia complain of an inability to sit still. Accompanying features include fidgeting, rocking back and forth, crossing and uncrossing the legs, or constant pacing. Motor activity relieves the inner subjective urge to move and, not surprisingly, the condition is frequently mistaken for agitation. The association of an inner urge and an outward motor response bears some resemblance to a tic, though akathisia differs in that the urge to move is constant and the motor component is continuous, stereotyped, and repetitive.

The pathophysiology of drug-induced akathisia is not understood, but may be related to blockade of nonstriatal dopaminergic pathways. Anticholinergic drugs are often ineffective in relieving the condition. Benzodiazepines may help. Often, it is necessary to reduce the dosage of the neuroleptic or substitute another class of compound.

**PARKINSONISM**

This is the most common neurologic side effect of neuroleptics, occurring in from 20 to 40% of patients treated with such agents. Symptoms, which usually appear in the first 3 weeks of treatment, are both dose-related and drug-related. The piperazine phenothiazines and butyrophenones are the compounds most often implicated in precipitating this syndrome, whereas the substituted benzamides such as sulpiride and thioxanthines are least often responsible. The condition is seen with increasing frequency with age and in those with underlying cerebral disease.

The clinical manifestations are identical to those of Parkinson's disease, with tremor, rigidity, postural abnormalities, and bradykinesia. Drooling is a frequent accompaniment. Bradykinesia, the earliest manifestation, is usually followed by rigidity, abnormalities of posture, and, lastly, resting tremor. Rigidity and tremor are usually symmetrical. An unusual variant seen following medium to long-term neuroleptic treatment is the occurrence of a 5 to 7 Hz perioral tremor, so-called rabbit syndrome.

The mechanism of drug-induced parkinsonism is blockade of striatal postsynaptic dopamine (D2) receptors, producing a functional deficiency of dopamine at those sites. Treatment of the condition involves either stopping or reducing the neuroleptic or alternatively introducing an anticholinergic agent. However, tolerance to the extrapyramidal effects of neuroleptics develops despite continuation of an offending agent. This phenomenon of tolerance may be related to pharmacokinetic factors, such as increased metabolism. Withdrawal of the antipsychotic drug usually leads to resolution of parkinsonism within a matter of weeks, though the condition may persist for 6 months or longer. One reason for this appears to be the persistent presence of active metabolites for up to 3 months after discontinuation of treatment.

**TARDIVE DYSKINESIA**

TD is a hyperkinetic involuntary movement disorder of diverse and widespread manifestations. The occurrence of the syndrome in association with 1957 with 1940s is most often encountered in patients treated with neuroleptic drugs. The condition usually presents in the first month of treatment. A delayed-onset variant, tardive dyskinesia, is reported in up to 25% of patients with TD.

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with neuroleptic medication was first described in 1957, shortly after the introduction into clinical practice of phenothiazine neuroleptics. Further observations of a hyperkinetic syndrome occurring in close temporal association to commencement of neuroleptic medication followed. The term “dyskinetic” was introduced by Faurbye. TD constitutes the most serious side effect of antipsychotic treatment by virtue of its disfiguring nature and its persistence.

The abnormal movements that comprise TD are coordinated, stereotyped, and rhythmic. Most common is cranial involvement, but limb and truncal involvement are also seen. Functional effects of TD include difficulties in speaking, swallowing, and breathing, and abnormalities of posture or gait. The clinical manifestations may be exacerbated by emotional arousal; they disappear during sleep. The earliest cranial manifestation is frequently a writhing movement of the tongue on the floor of the mouth. More marked facial involvement leads to tongue protrusion, often rapid protrusion and withdrawal (so-called flycatcher tongue), grimacing, lateral chewing jaw movements, and sucking or pursing of the lips. These symptoms may appear singly or in combination (buccolinguomasticatory [BLM] dyskinesia). Limb involvement consists of choreiform or jerky movements that may be accompanied by distal athetoid movements of the limbs. Truncal involvement includes writhing or ballistic movements, rhythmical movements of the body from side to side or rocking when the subject is seated. Multivariate statistical analyses of these movements identify two sub-syndromes of TD, a cephalic and a trunk/limb dyskinesia. Support for such fractionation comes from observations that the cephalic syndrome responds to increased neuroleptic dosage and worsens with anticholinergic treatment while the peripheral types may improve with anticholinergic and worsen with increased neuroleptic.

Although TD is an undoubted effect of long-term neuroleptic treatment, there is considerable controversy as to whether the occurrence of this condition in chronic psychiatric patients is due solely to the effects of neuroleptics, to the underlying disease process, or to an interaction of drugs with the underlying disease state. Central issues in this controversy are whether a condition akin to TD occurred in the preneuroleptic era and whether the prevalence of the condition has increased with increasing use of neuroleptics. There is very little information on the latter point, though there is considerable clinical evidence that conditions characterized by excess movements, akin to TD, were seen in the preneuroleptic era. Kraepelin described abnormal movements in chronic psychotic patients thus: “Connected with these are, further, smacking and clicking of the tongue . . . But besides we observe especially in the lip muscles, fine lightning-like or rhythmical twitchings, which in no way bear the stamp of voluntary movements. The same is the case in the tremor of the muscles of the mouth which appears sometimes in speaking . . .” However, it is uncertain whether these early descriptions are indeed from patients with primary schizophrenic illness or schizophrenic illness secondary to primary neurologic conditions, such as postencephalitic states. Furthermore, TD is described in patients receiving neuroleptics for conditions other than schizophrenia, such as manic-depressive illness.

The reported prevalence of TD in populations of patients receiving neuroleptic medication varies from 1 to 40%. Discrepancies in reported prevalence are partly attributable to variations in operational definitions of TD, with some early reports being based solely on the BLM triad. Other variables that may influence prevalence figures include age, duration, type, and dosage of medication. An accepted prevalence figure is 20% of patients on long-term neuroleptic treatment.

Risk factors for the development of the disorder that have emerged from epidemiologic surveys include age, female sex, and underlying cerebral disease or damage. An increased risk of developing the disorder is also reported in patients receiving concurrent anticholinergic drugs. The disorder is most often seen in schizophrenic patients but also occurs in other populations of neuroleptic-treated patients. Indeed, contrary to arguments for special association with schizophrenia, it has been suggested that patients with affective disorder exposed to neuroleptics are at greater risk of developing the disorder. The condition is also encountered in postencephalitic states, as a spontaneous condition in up to a quarter of the elderly population, during L-dopa therapy, and as minor manifestations in Wilson’s disease, Huntington’s disease, and Sydenham’s chorea. A state-dependent variant has been reported in association with the depressive phase of bipolar affective disorder.

TD is generally associated with medium to long-term exposure to neuroleptics but can occur with exposure as brief as several weeks. The piperazine side-chain and butyrophenone drugs are associated with an increased risk of developing the disorders while the substituted dibenzamides and newer antipsychotic agents such as clozapine are relatively risk free. The condition may first appear during withdrawal of neuroleptics: withdrawal dyskinesia. There are no consistent findings relat-
ing dosage of neuroleptic to risk of developing the syndrome.

The disorder needs to be distinguished from stereotypies and mannerisms of schizophrenia. The former are repetitive, pointlessly executed, normal movements, while the latter are bizarre, unnatural exaggerations of normal movements.

TD in its full expression may be persistent. However, reversal of the syndrome occurs in a third of patients on withdrawal of the neuroleptic. Evidence suggests that such spontaneous remission of TD is inversely correlated with age. Specific treatments for TD are lacking. An increase in neuroleptic dosage results in temporary suppression of symptoms. In view of a lack of effective treatments the focus must be on prevention.

There is little hard evidence that so-called drug holidays—that is, periods off neuroleptics—lead to a decreased risk of developing the condition. In susceptible individuals it is best to use neuroleptics with a decreased risk of inducing the condition, such as sulpiride or clozapine. In patients who have developed the condition, but in whom there are compelling clinical reasons to continue treatment, a switch to one of the low-risk agents is indicated.

The pathophysiology of the condition is not fully understood. Overstimulation of striatal dopamine systems is the mechanism mainly implicated. The theoretical explanation for dopamine overstimulation in the presence of DA antagonists invokes postsynaptic supersensitivity secondary to blockade of DA receptors. Experimental findings from animal models of TD uphold this hypothesis although other hypotheses have involved alteration of GABA.

**TARDIVE DYSTONIA**

Dystonic movements of late onset as a major side effect of neuroleptic medication have been recognized for almost 20 years. Tardive dystonia is considered a variant of TD rather than a separate clinical entity. Its clinical manifestations are those of a dystonia with sustained involuntary muscular contractions. Dystonic movements in the form of hyperextension or abduction of limbs, excessive lordosis, and pelvic rotation are frequent accompaniments of TD. In tardive dystonia the dystonic movements are the predominant feature. The condition resembles a primary dystonia and may be focal, segmental or generalized in distribution. A variant is so-called Meige's syndrome, which involves both a lower facial dystonia and blepharospasm, sometimes referred to as the orofacial-mandibular blepharospasm syndrome. As is primary dystonia, it is frequently unresponsive to drugs. The major risk factor is similar to that of TD, namely, prolonged exposure to neuroleptics. However, unlike the latter, it is more frequently encountered in young patients. A relationship between age of onset and bodily distribution of dystonic movements has been noted, with generalized dystonias tending to occur in the young while segmental or focal dystonias occur in older individuals.

The onset of the condition has been described after intervals of neuroleptic treatment varying from 3 days to 11 years. Prevalence data are sparse. One study of hospitalized patients with chronic illness found a figure of approximately 2%. As in TD, it may be masked by increases or remit following decreases or withdrawal of neuroleptics. In a proportion of cases it is persistent after withdrawal of drugs. Treatment is unsatisfactory. Strategies that may be helpful include antiparkinsonian drugs, anticholinergics, tetrabenazine, and benzodiazepines.

**NEUROLEPTIC MALIGNANT SYNDROME**

This is an uncommon but potentially fatal side effect of neuroleptic medication. Its infrequency and variable clinical features often lead to failure in detection. The full-blown syndrome develops over a matter of 48 to 72 hours. In the majority of cases onset follows primary exposure to neuroleptics, though patients developing neuroleptic malignant syndrome (NMS) may in some instances have had previous exposure to neuroleptics. The syndrome was named in 1968 by Delay though fatal reactions in association with neuroleptics were observed shortly after their introduction.

The clinical features include hyperthermia, extrapyramidal symptoms such as parkinsonism, rigidity, dystonia, and tremor, autonomic instability with tachycardia, diaphoresis, lability of blood pressure, tachypneic hypoventilation, alteration of consciousness, stupor, or coma. Dehydration is a feature of most cases on presentation.

Although most authors accept a pathogenic role for neuroleptics, there is a remarkably close resemblance between NMS and fulminating psychotic illnesses recognized before the neuroleptic era. A syndrome of acute catatonic delirium was reported as far back as 1832 by Calmeil and subsequent descriptions outlined potentially fatal psychotic illnesses with features that include hyperthermia, catatonia, and alteration of consciousness frequently ending in coma or death. Varying epithets, including lethal catatonia, catatonic delirious state, défie aigu, exhaustion syndrome, Stauder's lethal catatonia, and hypertoxic schizophrenia have been used to describe this syndrome.
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Follow-up studies of these catatonic-delirious states demonstrate an outcome similar to that of NMS. These early observations raise a question as to whether neuroleptics in themselves are necessary or sufficient causes for the development of NMS. A role for neuroleptics is suggested by the occurrence of the syndrome close to the time that they are started or increased in dosage. This association may, however, be spurious in that most psychotic disorders, which might have been possibly postulated as delirious catatonia, are likely nowadays to be treated early with neuroleptics.

More compelling evidence for a role for neuroleptics is that NMS is also seen in nonschizophrenic disorders following exposure to neuroleptics. Furthermore, withdrawal of neuroleptics may lead to recovery while reintroduction may lead to relapse of NMS. There have been suggestions that NMS can be considered a neuroleptic-induced iatrogenic form of lethal catatonia.

Laboratory findings, which may be entirely normal, include a polymorphonuclear leukocytosis in 70% of cases, raised muscle creatine (CK) in 92%, and myoglobinemia in 70%. Abnormalities of liver function tests are also reported in up to 70%, as is proteinuria in 90% of cases. Raised CK levels are also reported in psychotic patients; this could be construed as evidence that NMS is one facet of a spectrum of disorders for which elevated levels of this enzyme are a marker. Evidence of muscle necrosis on biopsy has been reported in up to half of patients affected. Complications of the syndrome include infection, rhabdomyolysis, renal failure (due to rhabdomyolysis and myoglobinuria), and pulmonary insufficiency. Investigations including electroencephalography, computed tomography, and analysis of cerebrospinal fluid are unremarkable.

The prevalence of NMS is difficult to assess given that the condition is often unrecognized. It is most frequently encountered in association with butyrophenones and piperazine phenothiazines. Estimates of its prevalence among neuroleptic-treated populations vary from 0.5 to 1.5%. The condition is reported as up to three times more common in males. Little is known concerning the primary pathologic features, though striatal and hypothalamic damage have been postulated.

A role for dopamine is likely in that the condition is seen with agents other than neuroleptics that alter dopamine function. The overall mortality from the condition is of the order of 20 to 30%. This may well be falling with earlier recognition and better management. Withdrawal of neuroleptic leads to recovery generally within 7 to 10 days. Symptomatic measures consist of rehydration, control of temperature, and maintenance of cardio-vascular and renal function. Dopamine agonists are used on the assumption that the syndrome is at least partly due to dopamine blockade. Treatments of this nature with reported beneficial effects include bromocriptine, amantadine, and dantrolene.

LITHIUM

The naturally occurring salt, lithium carbonate, is one of the most effective treatments in psychiatry. Its prime role is in the treatment of cyclic mood disorders, both unipolar and bipolar. Its therapeutic effects are seen with dosages that give a serum level of between 0.5 and 1.2 mEq/liter. Neurologic side effects from lithium are prominent with increasing serum levels above 1.2 mEq/liter. Beyond this range, there develops a coarse tremor, ataxia, dysarthria, drowsiness, hyperreflexia, seizures, myoclonus, coma, and eventually death. Occasionally, the signs may be unilateral, suggesting an alternative diagnosis. These side effects are well recognized and careful monitoring of serum lithium levels should prevent their development. Less widely recognized are neurologic reactions occurring within the therapeutic range. The most prevalent of these is a fine hand tremor which may be a transient effect on commencement of lithium or a long-term effect. Less common are instances of parkinsonism.

The most serious neurologic side effects are rare cases of a neurotoxic reaction in patients on combined lithium and neuroleptic therapy, particularly haloperidol. This is characterized by extrapyramidal and cerebellar signs which may be permanent. Lithium used concurrently with neuroleptics in bipolar affective patients may also increase the risk of developing TD in this group.

ANTIDEPRESSANTS

MONOAMINE REUPTAKE INHIBITORS

This broad class of agents constitutes the mainstay treatment of affective disorders and includes the tricyclics, tetracyclics, and the newer selective monoamine reuptake inhibitors (MAOIs), such as 5-hydroxytryptophan (5-HT) reuptake inhibitors. Since this grouping contains a wide diversity of pharmacologic compounds, many with a broad spectrum of central effects, the range of side effects is great. However, as a general rule, these compounds are devoid of any permanent neurologic sequelae. This is somewhat surprising given.
the structural similarity between the tricyclics and the phenothiazine neuroleptics.

Neurologic side effects at toxic levels or overdose are largely attributable to anticholinergic effects, which include confusion, distractibility, hallucinations, slurred speech, insomnia, and coma. At therapeutic levels, like the neuroleptics, the tricyclics and tetracyclics are associated with peripheral antimuscarinic effects, including dry mouth, blurred vision, delayed ejaculation, and urinary retention. Trazodone may cause priapism and permanent impotence. Central effects are mainly dose related and are seen especially in the elderly. Confusion, reported in 10% of patients, is possibly related to the anticholinergic effects of some MAOIs. A fine tremor is seen in approximately 5% of patients on tricyclics, but extrapyramidal effects proper are extremely rare. Alteration of seizure threshold is a potential side effect of all drugs in this class. Isolated cases of NMS are also reported in association with this class of antidepressants.

**MONOAMINE OXIDASE INHIBITORS**

This chemically broad category of drugs shares a common property of inhibiting oxidative deamination of monoamines. Two subclasses are recognized, with relatively selective potencies for inhibition of monoamine oxidase (MAO) A and B, the two subtypes of MAO enzyme. All compounds in this group are irreversible (“suicide”) inhibitors of MAO.

Toxic effects are seen following overdose and at therapeutic levels. The former consist of agitation, hyperreflexia, hyperpyrexia, hallucinations, and convulsions. At therapeutic levels, neurologic side effects include tremor, insomnia, hallucinations, and confusion. Peripheral neuropathy is seen in a proportion of patients exposed to the hydrazine group of MAO inhibitors.

**ANTIANXIETY AGENTS**

The main compounds in clinical use for the management of anxiety states are the benzodiazepines. Indeed, they comprise the most widely prescribed psychotropic agents. Newer antianxiety compounds, particularly with affinities for central serotonergic receptors, are under evaluation in clinical practice. The principal adverse effects of these agents relate to their potential for causing dependence and abuse. Therefore a physical withdrawal syndrome, of which seizures may be a component, is frequently encountered in patients taking these compounds on a medium to long-term basis. In patients stabilized on these compounds there are remarkably few side effects. Neurologic side effects are mild and consist of impaired psychomotor performance and impairment of attention on vigilance tasks.

**ELECTROCONVULSIVE THERAPY**

Since its introduction into psychiatry, this treatment has generated a great deal of controversy with regard to both its efficacy and its side effects. Neurologic side effects are few. They consist principally of memory disturbance. Coarse brain damage as a result of ECT has frequently been claimed but remains unproven.

Transient memory loss, both retrograde and anterograde, is a well recognized and uncontested immediate side effect of ECT. A major component of these deficits can be attributed to the effect of severe depression per se on memory functioning. Long-term memory impairment is a frequent subjective complaint of patients who have received ECT. An objective basis to these complaints is established. A disturbance of personal biographic memory is seen in a proportion of patients following ECT. It is less marked with unilateral, nondominant hemisphere (as opposed to bilateral) ECT.

**PSYCHOSURGERY**

Psychosurgery is now relatively rare in psychiatry. In clinical practice, however, one still encounters patients who have been exposed to this type of intervention. In Great Britain the number of procedures carried out fell from 70 in 1979 to 15 in 1986. It remains a highly controversial intervention in view of the nature of the procedure, its scientific justification, and the ethical issues involved. Many practicing psychiatrists disagree entirely with its use. Those who see a role for psychosurgery limit its usage to patients with severe and intractable anxiety, obsessive disorders, and depressive illness that has not responded to other therapies. Procedures now in use are entirely stereotactic, producing lesions of the inferior frontal white matter (subcaudate tractotomy) and anterior cingulate gyri. The former procedure is performed for affective disorders, anxiety, or depression, while the latter is indicated in intractable obsessive disorders.

There are many problems in evaluating neurologic side effects of psychosurgery particularly as one is dealing with an unusual and atypical population. Furthermore, there is a striking paucity of
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independent studies evaluating the effectiveness and outcome of the procedure. Most data are therefore from centers with a vested interest in the procedure. Epilepsy is reported in up to 3% of patients who have had the procedure. Personality change has been reported in up to 7%. Curiously, for a procedure that damages cerebral tissue, there are no reports of a fall in intelligence or more focal intellectual deficits.

CONCLUSIONS

The overall frequency of neurologic side effects resulting from psychiatric treatments is low when viewed in the context of the widespread use of psychotropic agents in developed countries. Among psychotropic drugs, the most hazardous, with regard to neurologic side effects, are the neuroleptics. Although side effects from neuroleptics are generally reversible, there is a number of responses that may be irreversible or even fatal. This makes imperative the judicious use and careful supervision of such compounds. However, the potential benefits of neuroleptics in the treatment of the psychoses still far outweigh any risks associated with their use.

The development of more specific treatments for the psychoses is a major endeavour within psychiatry and the pharmaceutical industry. Advances in neuroimaging and molecular genetics are having a major impact on the scientific underpinnings of psychiatry, leading to the acquisition of more precise knowledge concerning pathophysiological mechanisms. The impact of such knowledge on therapeutic developments is difficult to gauge at present. Therapeutic advances in psychiatry, until now, have largely been due to serendipity, though there is every reason to feel optimistic that treatments based on precise knowledge of disease processes are within our grasp.

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