American Handbook of Psychiatry

Withdrawal Effects from Psychotropic Drugs

George Gardos
Jonathan O. Cole
Daniel Tarsy

Withdrawal Effects from Psychotropic Drugs

George Gardos, Jonathan O. Cole, and Daniel Tarsy

e-Book 2016 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 7* edited by Silvano Arieti

Table of Contents

WITHDRAWAL EFFECTS FROM PSYCHOTROPIC DRUGS

George Gardos, Jonathan O. Cole, and Daniel Tarsy

The term "withdrawal effects" tends to conjure up images of drug dependent persons in the throes of severe, invariably unpleasant, and at times dangerous abstinence reactions to opiates or barbiturates. There is much less attention paid to the not so dramatic, but nonetheless quite common, phenomenon of withdrawal symptoms occurring when prescribed psychotropic drugs are abruptly discontinued. Awareness of this problem could prevent a great deal of unnecessary pharmacotherapy. For instance, a patient on maintenance drug therapy may repeatedly attempt to discontinue the drug abruptly and then conclude from the resulting withdrawal symptoms that indefinite drug therapy is needed. Physicians do not always terminate drug therapy in a manner that minimizes the likelihood of withdrawal effects.

Classes of drugs will be discussed separately in the following sections. Special mention will be given to situations in which simultaneous discontinuation of two or more drugs may pose unusual problems. This chapter covers only psychotherapeutic drugs and avoids dealing with the vast literature on the phenomena of abstinence from drugs of abuse.

Antipsychotic Drug Withdrawal

Very little attention has been paid to the manner in which antipsychotic drugs are discontinued in clinical practice. As often as not, drugs are stopped abruptly with no expectation of adverse consequences other than the possibility of psychotic relapse. In fact, however, a number of autonomic, behavioral, and neurological symptoms may occur in the post-withdrawal days and weeks. The importance of recognizing withdrawal symptoms and distinguishing them from psychotic relapse cannot be overemphasized.

Somatic Withdrawal Symptoms

The literature on antipsychotic drug discontinuation shows striking variations in the incidence and severity of withdrawal phenomena. Several studies reported no withdrawal symptoms, although it is entirely possible that since these studies focused on other issues, withdrawal phenomena may have been missed. When abrupt antipsychotic drug withdrawal is carried out in a carefully controlled design, statistically significant increases in withdrawal symptoms can be observed. A placebo effect is unlikely to play a role in the withdrawal syndrome: Battegay found no lessening in the prevalence of symptoms between patients switched to placebo and patients withdrawn from antipsychotics without placebo substitution.

Common withdrawal symptoms, as reported in relevant publications, include: nausea, vomiting, sweating, insomnia, restlessness, dizziness, and

headache. Occasionally tachycardia, faintness, “flu-like” symptoms such as feeling achy or hot and cold, rhinorrhea, abdominal pain, diarrhea, malar flushing, numbness, or nightmares have been reported. The clinical picture for the individual patient is unpredictable: any one or several symptoms may be reported with varying severity.

Typically, symptoms appear on the first, second, or third day after drug discontinuation, but may occasionally be delayed as much as one to two weeks. Symptoms usually peak during the first week, followed by a gradual attenuation and spontaneous recovery.

Age appears to be an etiological factor: older patients show high prevalence of symptoms. Female patients have been found to show significantly higher rates of withdrawal symptoms than male patients. Abrupt drug withdrawal is more likely to produce withdrawal symptoms than gradual withdrawal. Dosage of the antipsychotic drug before withdrawal, however, does not appear to be related to symptom prevalence. The anti-muscarinic anticholinergic effect of the withdrawn antipsychotic often determines whether or not withdrawal symptoms will occur. Luchins and associates reviewed the literature and found a highly significant association between anti-muscarinic potency and the number of patients showing withdrawal symptoms. Thus, of the standard antipsychotics in the United States, Thioridazine and chlorpromazine account for most of the reported

somatic withdrawal symptoms.'' On the other hand, antipsychotic drugs with low muscarinic potency, such as piperazine, phenothiazines, and haloperidol, are less likely to induce somatic withdrawal symptoms and in fact few such cases have been published. Anti-parkinsonism drugs, by virtue of their strong anti-muscarinic effects, frequently induce withdrawal symptoms. Simultaneous withdrawal of antipsychotic-anti-Parkinson drug combinations often result in somatic symptoms that are partly, if not wholly, a result of anti-Parkinson drug withdrawal.

The neuropharmacological changes underlying somatic withdrawal manifestations appear to represent mainly a cholinergic hypersensitivity reaction. It is thought to be a rebound phenomenon resulting from prolonged treatment with drugs with strong anticholinergic properties. This hypothesis is supported by studies that showed that physostigmine, a powerful cholinergic agent, can induce most of the commonly noted somatic withdrawal symptoms which, in turn, can be abolished by anticholinergics. However, when antipsychotics with minimal anti-muscarinic potency are withdrawn, a cholinergic rebound probably does not occur. In fact, as Luchins and associates have recently demonstrated with chronic haloperidol treated mice, the converse may be true in that haloperidol withdrawal may induce a state of cholinergic sub-sensitivity.

The principal features of somatic withdrawal symptoms are

summarized in Table 18-1. Of particular importance to the practitioner is the self-limited nature of these symptoms and their strong association with anticholinergic drugs such as Thioridazine or chlorpromazine. Clinical management in mild cases simply requires reassurance of the patient. In more severe cases, anticholinergic compounds such as Benztropin or diphenhydramine may provide specific remedies. Since the symptoms usually last only a few days and may induce secondary anxiety, diazepam or other benzodiazepines may have nonspecific utility in supporting the patient while the symptoms fade. If the somatic withdrawal effects are severe or are combined with neurological withdrawal symptoms, retreatment with the previously withdrawn antipsychotic is called for. More gradual dose tapering may then be attempted at a later date.

Extrapyramidal Complications of Antipsychotic Drug Withdrawal

The clinical literature provides ample evidence for the principle that every extrapyramidal symptom that can be produced by drug administration may also be seen upon drug withdrawal.

Parkinsonism

There is almost universal agreement among experts that drug-induced parkinsonism tends to improve following antipsychotic drug withdrawal. However, the extent and the time course of improvement remains unresolved.

Depending upon the duration of post-withdrawal observation, parkinsonian signs have been found to disappear in a few weeks, improve substantially within three to six months,- or remain unchanged sixteen weeks after antipsychotic withdrawal.

Case reports in which severe acute extrapyramidal symptoms occurred following withdrawal usually involve simultaneous withdrawal of antipsychotic and anti-Parkinson drugs. The more rapidly excreted anti-Parkinson drug leaves the antipsychotic drug free to exert its neuroleptic effect unopposed. Occasionally, the extrapyramidal reaction is markedly delayed. In a sixty-four-year-old woman, a dystonic reaction occurred twenty-one days after drug withdrawal, while in a nineteen-year-old man, withdrawal akinesia lasted nineteen days following low dose phenothiazine therapy of relatively brief duration. Alpert and associates described a case of paradoxical worsening of extrapyramidal signs produced by anti-Parkinson drugs following discontinuation of chlorpromazine, Trifluoperazine, and trihexyphenidyl. These case reports suggest that the clinical course of withdrawal tremor, rigidity, akinesia, and dystonia may not be a simple function of antipsychotic drug effects and that a special vulnerability exists in certain individuals to extrapyramidal effects in the post-withdrawal weeks.

Table 18-1 Somatic Symptoms of Antipsychotic Withdrawal

Common symptoms:	nausea, vomiting, sweating, insomnia, restlessness
Onset:	typically one to three days after drug withdrawal

Duration:	one to three weeks
Type of AP:	Thioridazine or chlorpromazine, rare with drugs of low anti-muscarinic potency
Pharmacological substrate:	cholinergic rebound
Treatment:	reassurance, tranquilizers, anticholinergics, rarely with resumption of anti-psychotic

Dyskinesias

Choreoathetotic dyskinetic movements tend to increase in intensity or may appear for the first time following antipsychotic drug withdrawal. *Withdrawal dyskinesia* is a self-limiting syndrome initially indistinguishable from tardive dyskinesia. Cases of withdrawal dyskinesia have been reported following withdrawal of chlorpromazine, fluphenazine, mesoridazine, and haloperidol. In these reports, dyskinesias were noted within days of drug withdrawal and lasted from one to twenty-two weeks, but in all cases, complete resolution of the syndrome was observed.

While not all antipsychotic compounds have been shown to produce withdrawal dyskinesias, it is likely that all dopamine-blocking antipsychotics may do so. Degkwitz and associates noted a sex difference: withdrawal dyskinesias tended to develop later and lasted longer in female than in male patients, in contrast to post-withdrawal parkinsonism which tended to resolve faster in female patients.

Dyskinesias that become obvious only as a consequence of drug withdrawal and persist for many weeks can be regarded as a type of tardive dyskinesia. The term “covert dyskinesia” is sometimes applied to this syndrome to emphasize that dopamine-blocking antipsychotics often mask an underlying dyskinesia which may be uncovered by drug withdrawal. The prevalence of covert dyskinesia varies greatly, but, in some studies, it has been strikingly high: Degkwitz and Wenzel found 47 such patients (39 percent) in a double-blind drug withdrawal study of 119 persons. Escobar and Tuason reported that eight out of nine patients who were on oral fluphenazine prior to withdrawal developed clinically significant dyskinesias. Female sex and higher pre-withdrawal dosage have been reported to be contributing factors.

The natural course of covert dyskinesia is difficult to establish. In some instances, the emerging dyskinesia is massive and may be life threatening, and quick resumption of antipsychotic drug therapy is the indicated clinical course. Psychotic decompensation not infrequently disrupts the drug-withdrawal period and results in retreatment with antipsychotics.’- Therefore, in many cases of dyskinesia following withdrawal, the resumption of drug therapy makes it impossible to establish whether the dyskinesia would have been self-limiting (withdrawal dyskinesia) or persistent (covert dyskinesia). In general, the prognosis of covert dyskinesia is quite similar to tardive dyskinesia: chronic, older patients with prolonged exposure to

antipsychotics tend to develop persistent dyskinesias,' whereas younger patients who have undergone shorter courses of treatment often show reversible dyskinesias.

An intriguing aspect of withdrawal dyskinesias is their apparent association with psychotic relapse in that patients with dyskinesias may be more prone to decompensation,'' while no relationship was found between disappearance of parkinsonism and psychotic relapse. At present, this is more a clinical observation than an established statistical correlation, but it raises fundamental questions about the way drugs exert antipsychotic and neuroleptic actions and will be discussed later. The extrapyramidal effects of antipsychotic withdrawal are summarized in table 18-2.

Psychotic relapse

Two cases of delirium associated with antipsychotics and resembling alcohol withdrawal have appeared in the literature. A twenty-seven-year-old man developed delirium with visual and auditory hallucinations twenty hours after abrupt discontinuation of haloperidol. Within three days, the symptoms abated spontaneously. A forty-six-year-old man developed an acute brain syndrome lasting seven days two days after thiothixene withdrawal. These isolated instances notwithstanding, the appearance of psychotic manifestations after antipsychotic drug withdrawal almost invariably heralds

psychotic decompensation. The time lag between withdrawal and relapse is highly variable. A number of controlled studies of antipsychotic drug withdrawal showed that relapse rates occurred at a constant rate during the first twelve months, declining thereafter. But, as long as two years after drug discontinuation, placebo relapse rates still exceeded relapse rates for drug-maintained schizophrenics.'' Clearly the prediction of the time of onset of psychotic decompensation in the individual patient is problematical. Distinct and recognizable stages of decompensation have been described: (1) denial and anxiety; (2) depression and intensification of defense mechanisms; (3) internal chaos; and (4) subjective relief. Early symptoms of decompensation such as anxiety, tension, and insomnia overlap somatic withdrawal symptoms; differentiating these two phenomena may be as difficult as it is clinically important.

Table 18-2 Extrapyramidal Effects of Antipsychotic Drug Withdrawal

			DYSKINESIA
	DRUG-INDUCED PARKINSONISM	"WITHDRAWAL DYSKINESIA"	"COVERT DYSKINESIA"
Symptoms	Tremor, rigidity, dystonic reactions, akinesia	Choreoathetosis, motor restlessness	Choreoathetosis, tics, grimaces
Etiology	Continuation of already existing syndrome Simultaneous withdrawal of anti-Parkinson drugs	Tends to occur after relatively brief drug exposure	Tends to occur after prolonged drug therapy
Onset	Within a few days, occasionally delayed two to three weeks	Usually within days	Usually within two weeks

Course	Slow, gradual improvement	Spontaneous recovery	Variable: may remit, persist or intensify
Management	Short-tear treatment with anti-Parkinson drugs may be needed	Occasional patient may need sedative-hypnotic or benzodiazepine	Retreatment with any-psychotics in severe cases, no treatment for mild cases, anti-dyskinesia drugs for intermediate cases

Tardive Psychosis

Several recent reports have suggested that psychotic phenomena that are not simply attributable to a return of schizophrenic symptoms may occur following drug withdrawal. Sale and Kristall described a twenty-one-year-old woman with obsessional symptoms and anxiety who developed what later progressed into chronic schizophrenia following withdrawal of chronically administered chlorpromazine. Forrest and Fahn observed an array of psychotic and other symptoms on antipsychotic withdrawal that were distinct from the original symptoms for which patients were treated. The symptoms subsided with resumption of drug therapy.

Forrest and Fahn considered these symptoms to result from the drug withdrawal phenomena and labeled the syndrome “tardive dysphrenia.”

Davis and Rosenberg presented evidence from animal studies for super-sensitivity in mesolimbic dopamine receptors and suggested that cases of withdrawal psychosis might reflect mesolimbic dopamine super-sensitivity. McCarthy raised the issue of whether reversible “withdrawal psychosis” or

persistent “tardive psychosis” might not occur analogous to withdrawal and tardive dyskinesias, reflecting limbic hypersensitivity to dopamine. Chouinard and Jones presented ten cases of what they called “super-sensitivity psychosis.” These schizophrenic patients were treated with depot fluphenazine but appeared to require increasing doses for therapeutic effect and showed positive schizophrenic symptoms following decrease in dosage just before the next scheduled injection, or after missing one or two doses. Chouinard and Jones concluded that neuroleptic-induced mesolimbic dopamine super-sensitivity accounted for their clinical findings. The thrust of these reports is that significant neuropharmacological changes may occur during antipsychotic drug treatment in areas other than the striatum, and that during drug withdrawal, these changes may be manifested in behavioral and occasionally even in neuroendocrine changes. For example, the association shown in two studies between lower prolactin levels and greater clinical deterioration after antipsychotic discontinuation points to the existence of a subgroup of schizophrenic patients with an overactive and labile dopaminergic system. These patient characteristics may play an important role in the production of withdrawal phenomena.

Although the notion of “tardive psychosis” is an intriguing one and of great practical concern, it is certainly not yet a proven entity. It has been pointed out that “relapse” following antipsychotic drug withdrawal increases in a linear fashion during the first year at a rate of about 7 to 15 percent per

month. It is therefore likely that in any large clinic population of schizophrenic patients, a certain small proportion will show reemergence of psychosis very shortly after drug withdrawal. Whether the psychiatric characteristics of these patients can be differentiated from a new and superimposed withdrawal psychosis as has been claimed remains to be confirmed by future studies.

Antipsychotic Withdrawal in Children

The same types of withdrawal phenomena may be observed in children as in adults. Yepes and Winsberg reported cases with extensive symptomatology. The first patient was a nine-year-old boy who, following abrupt withdrawal of chlorprothixene 150 mg/d, developed restlessness and insomnia (first day); nausea and vomiting (fourth day); and hemiballismus, dystonia, and severe posturing of the arms and face (sixth day). The second patient, also a nine-year-old boy, when withdrawn from Thioridazine 125 mg/d, developed irritability (first day); stomachaches (tenth day); dyskinesia (fourteenth day); and nausea and vomiting (twenty-first day). Vomiting was severe and lasted twelve days, while the extrapyramidal disorder persisted up to ninety days. Polizos and associates studied the effects of abrupt antipsychotic drug withdrawal in thirty-four schizophrenic children, six to twelve years old. Fourteen children developed choreiform dyskinesias (mainly involving the extremities, trunk, and head) and ataxia appearing one

to fifteen days after withdrawal. In half of the affected children, the dyskinesias remitted spontaneously within five weeks; in the other children, drugs had to be resumed because of massive psychotic relapse. The withdrawal dyskinesias of children are thought to be reversible.

Neuropharmacological Considerations

Withdrawal symptoms tend to be mirror images of the drug-induced changes that occur during treatment. For example, administration of chlorpromazine produces sedation, fatigue, and hypokinetic extrapyramidal effects, while removal of the drug may induce insomnia, restlessness, and hyperkinetic extrapyramidal effects. In pharmacological terms, the issues of neurotransmitter blockade, tolerance, and super-sensitivity may underlie the observed somatic and behavioral changes.

The interruption of synaptic transmission in either the peripheral or central nervous system may result in a state of denervation super-sensitivity to administration of the blocked neurotransmitter or its agonist. Because of greater accessibility, denervation super-sensitivity has been studied in more detail in the peripheral than the central nervous system. Preganglionic nerve section, ganglionic lesions, peripheral nerve section, and pharmacological interference with synaptic transmission have been utilized to effect denervation super-sensitivity . An interesting example of the importance of

denervation super-sensitivity in the peripheral autonomic nervous system occurs in patients with angina and hypertension who are treated chronically with propranolol, an antagonist at beta-adrenergic receptor sites. When propranolol is abruptly withdrawn, unstable angina, myocardial infarction, and cardiac irritability sometimes occur. One proposed explanation for this is increased sensitivity of cardiac tissue to beta-receptor agonists. The observation that the treatment of rats with propranolol for two weeks leads to a 100 percent increase in the number of beta-adrenergic receptors is compatible with the hypothesis of denervation super-sensitivity .

The extrapyramidal neurologic effects and possibly the therapeutic antipsychotic effects of neuroleptic drugs are believed to derive from their capacity to block dopamine mediated synaptic transmission. Evidence for the capacity of neuroleptic drugs to block dopamine receptors derives from their antagonism of behavioral and neuroendocrine effects of dopamine agonists, their antagonism of dopamine-sensitive adenylate cyclase in caudate and limbic brain tissue, and the capacity of neuroleptic drugs to interfere with the binding of radioactively labeled ligands such as tritiated dopamine, apomorphine, and haloperidol to dopamine receptor sites.

Dopamine mediated projections lie in several discrete brain regions including pathways between midbrain and basal ganglia (the nigrostriatal tract), regions of the limbic forebrain, areas of temporal and prefrontal

cerebral cortex closely associated with the limbic system, and the hypothalamic-pituitary system. Although unproven, it is currently considered that extrapyramidal effects of neuroleptic drugs are due to dopamine blocking effects in the basal ganglia, while antipsychotic efficacy relates to dopamine-blocking effects in limbic nuclei and/or limbic cortex. When given acutely, the effect of neuroleptic drugs on dopamine neurotransmission is to increase the firing rate of dopamine neurons and to increase the synthesis, release, and metabolic turnover of dopamine in dopaminergic neurons. These effects may be viewed as compensatory responses by an adaptive neuronal system seeking to maintain adequate dopamine neurotransmission in response to dopamine receptor blockade.

When neuroleptic drugs are administered to animals on a more chronic basis, there is a gradual reduction in the neuroleptic-induced acceleration of dopamine turnover, such that, within seven days, following neuroleptic administration, dopamine turnover remains at baseline levels or is even reduced. Following a very similar time course, the capacity of neuroleptic drugs to produce catalepsy or block apomorphine induced stereotyped behavior in rats also becomes diminished. This loss of neuroleptic effect with repeated administration has been referred to as tolerance. One possible explanation for appearance of tolerance to neuroleptic effects is the development of enhanced sensitivity of dopamine receptors to dopamine. This gains support from repeated observation that chronic treatment of mice,

rats, or guinea pigs with drugs antagonistic to dopamine followed by their discontinuation produces increased behavioral responsiveness to dopamine agonists not accountable by other pharmacologic or pharmacokinetic mechanisms. This effect, presumably representing the development of functional super-sensitivity to dopamine in the brain, requires no more than several days of treatment with a neuroleptic drug and persists for several weeks with some evidence that the duration of this effect parallels the duration of pretreatment with neuroleptic drug. Supporting this behavioral evidence for denervation super-sensitivity of dopamine receptors have been changes in dopamine receptor binding which have been produced by chronic neuroleptic treatment. Several laboratories have demonstrated that following a course of neuroleptic pretreatment identical to that which produces behavioral super-sensitivity , striatal and limbic dopamine receptors increase in number and display enhanced affinity for radioactively labeled ligands which bind at dopamine receptor sites. Neurophysiologic studies have also shown that chronic treatment of rats with haloperidol produces a significant increase in the sensitivity of caudate neurons to microiontophoretically applied dopamine. The fact that similar behavioral, biochemical, and neurophysiological alterations have been observed following surgical lesioning of dopamine neurons, supports the concept that they reflect changes in receptor sensitivity brought about by interference with dopamine neurotransmission. On the basis of the aforementioned studies, it is suggested

that chronic neuroleptic treatment results in a compensatory increase in affinity and numbers of striatal dopamine receptors which offsets the effects of dopamine receptor blockade.

Since it has been the general clinical impression that patients do not become tolerant to the antipsychotic efficacy of neuroleptic drugs, it has been assumed that tolerance and super-sensitivity phenomena were restricted to the nigrostriatal system. Observations that drug-induced parkinsonism and acute dystonia tend to occur relatively early in treatment and become less frequent and severe with continued drug exposure, while transient withdrawal dyskinesias and persistent tardive dyskinesia appear later in treatment, support this concept.

In the case of the hypothalamic dopamine system, there is evidence that in both animals and man tolerance and dopamine super-sensitivity fail to develop with chronic neuroleptic treatment.' Evidence concerning tolerance and super-sensitivity in dopaminergic limbic nuclei and cortex has been less consistent, however. In early studies, chronic neuroleptic treatment produced a persistent increase in dopamine turnover in mesolimbic and mesocortical dopamine projections, suggesting absence of tolerance in this system. However, more recent studies have indicated that with chronic treatment, the neuroleptic-induced increase in dopamine turnover does subside in limbic nuclei, indicating a tolerance for this effect similar to that which occurs in the

striatum. Muller and Seeman reported an increase of dopamine binding sites in both striatal and mesolimbic regions following chronic neuroleptic treatment, while in two other studies, long-term neuroleptic treatment was found to increase the locomotor response of dopamine injected directly into the nucleus accumbens but not the striatum.

In humans, cerebrospinal fluid homovanillic acid (HVA), a metabolite of dopamine, is increased following neuroleptic treatment but returns toward normal after three weeks of continued drug exposure. Since cerebrospinal fluid HVA is derived from periventricular structures, its concentration may not reflect levels in other brain regions. Further studies in rodents, nonhuman primates, and also in man, all suggest, in fact, that tolerance to the effects of neuroleptic drugs on brain HVA concentration develops in midline nuclei such as the caudate nucleus and deeper limbic nuclei, but not in cortical regions such as cingulate, temporal, dorsal frontal, and orbital frontal cortex. Because of this sustained biochemical change in cortical dopamine metabolism with evidence of tolerance, it has been concluded that it may be in these brain regions that antipsychotic drugs produce their therapeutic effect.

Prevention of Withdrawal Symptoms

Antipsychotic drug withdrawal symptoms may be highly unpleasant, and, in rare instances, a severe withdrawal dyskinesia may be serious and life

threatening. Furthermore, withdrawal symptoms may obscure signs of early relapse, and, conversely, they may be mistaken for signs of psychotic decompensation. Avoidance of withdrawal symptoms, therefore, becomes an important goal. The following guidelines spell out the technique of withdrawal that may minimize the risk of such symptoms.

1. Withdrawal should be gradual rather than abrupt. Step-wise, gradual dose reduction will probably circumvent most withdrawal symptoms. In chronic drug-treated schizophrenics, the process of drug withdrawal may be spread over several months, delaying the onset and probably reducing the risk of psychotic relapse.

2. Anti-Parkinson drugs should be continued. Patients withdrawn from antipsychotics may develop a transient hyper-cholinergic state which produces somatic withdrawal symptoms. Continuation of anti-Parkinson drugs in patients on antipsychotic-anti-Parkinson combinations for one-two weeks beyond antipsychotic withdrawal may eliminate somatic symptoms as well as the recurrence of drug-induced parkinsonism.

Anti-Parkinson Drugs

The major therapeutic indication for anti-Parkinson drugs (APK) in psychiatry is the prevention or control of the extrapyramidal side effects of antipsychotic compounds. The most frequently used APK in the United States

are anticholinergics (trihexyphenidyl, procyclidine, Biperiden), anti-muscarinic antihistamines (Benztropin, diphenhydramine), and dopamine agonists (amantadine). These drugs are rarely, if ever, administered to psychiatric patients without antipsychotic drugs, and when the latter are discontinued, APK are usually withdrawn as well. As stated in the previous section, the somatic and parkinsonian symptoms following withdrawal of high potency antipsychotic drugs are usually due to the simultaneous withdrawal of anti-Parkinson drugs.

Withdrawing anti-Parkinson drugs alone while continuing antipsychotic drug treatment is frequently attempted in clinical practice in order to ascertain whether APK are still required. Surprisingly often, however, one finds that patients are most reluctant to part with their APK. In some cases, the desire to continue is undoubtedly related to the abuse potential of some APK, particularly trihexyphenidyl. Adverse behavioral, neurological, and mood changes may also occur on APK withdrawal and probably explain why some patients would rather stop their clearly essential antipsychotic drug than the supposedly unnecessary APK.

Specific withdrawal effects have been investigated in open as well as double-blind placebo-controlled studies of APK discontinuation. Most studies have focused on extrapyramidal symptoms while only a few have included assessment of psychopathology or mood.

Reappearance of Drug-induced Parkinsonism

There is a wide divergence of research results with regard to the frequency with which extrapyramidal symptoms reappear after APK withdrawal. Relapse rates (that is percentage of patients developing symptoms of parkinsonism) range from 8 to 80 percent in published studies of APK withdrawal. The most common symptoms of parkinsonism, namely tremor and rigidity, were usually focused on and were reported accurately. Akinesia, however, tended to be overlooked in some studies and to be underreported. Rifkin and associates found that akinesia occurred in 27 percent of patients following procyclidine withdrawal. Other factors that may account for the wide variation in relapse rates include variations in the populations studied, variations in the tolerance for milder extrapyramidal symptoms (that is, differing criteria for "relapse"), and drug type and dosage differences of both antipsychotics and APK.

The onset of parkinsonism was usually within two weeks and nearly always within four weeks of APK discontinuation. In a carefully documented study, Pecknold and associates found that symptoms first appeared an average of twelve and three-tenths days after APK withdrawal. Trihexyphenidyl or Biperiden were found to produce symptoms sooner than Benztropin withdrawal, reflecting the slower metabolism of Benztropin. No consistent differences were observed between placebo-controlled double-

blind studies and open trials. Two studies by Roy and associates, in which both placebo and no APK control groups were employed, produced conflicting results. No consistent relationship was demonstrated between antipsychotic dosage and extrapyramidal symptoms following APK withdrawal. Older age was associated with re-emergent parkinsonism in one study. Longer pre-withdrawal APK treatment was found to be correlated with lower relapse rates in three studies. Previous occurrence of extrapyramidal symptoms was found to predict post-withdrawal parkinsonian symptoms; thus therapeutic use of APK is more likely to lead to parkinsonism after withdrawal than prophylactic drug administration. No obvious differences were noted between the various anti-Parkinson drugs in their extrapyramidal withdrawal effects.

Somatic Withdrawal Symptoms

The frequent occurrence of somatic symptoms such as nausea, vomiting, and insomnia following withdrawal of antipsychotic drugs with marked anticholinergic effects was discussed previously. Since these symptoms are believed to reflect a cholinergic rebound, they may also be expected to result from the removal of anticholinergic anti-Parkinson drugs. Kruse was probably the first investigator to document somatic withdrawal reactions from APK. Specific withdrawal symptoms described in the literature include restlessness, nausea, dizziness, aches and pains, agitation, and stiff joints.

Somatic withdrawal symptoms have also been documented following the simultaneous withdrawal of butaperazine and Benztropin . The time course and treatment of the somatic withdrawal symptoms from APK are broadly the same as after antipsychotic withdrawal.

Mood Changes

The appearance of dysphoric symptoms is at times a striking effect of APK withdrawal. When specifically looked for, dysphoric symptoms turn out to be quite common. In a double-blind placebo-controlled study, Jellinek and associates found that out of twenty-four APK withdrawn patients, seven developed anxiety, two complained of fatigue, and one became depressed. In the often quoted study by Orlov and associates, the authors found ten out of seventy-eight patients to have complained about and resisted APK withdrawal. The authors attributed this to psychological dependence, however, these patients may have experienced genuine dysphoria. Depression has been noted by some authors to occur after APK withdrawal, particularly in connection with akinesia. The association of these two conditions has led to the concept of akinetic depression. It derives some support from the strong statistical association between parkinsonism and depression and suggests similarities in the underlying pathophysiology. The adverse mood changes from APK withdrawal suggest that APK may possess psychotropic properties, possibly antidepressant effects, at least in some

patients.

Improvement in Dyskinesia

On withdrawal of APK, the characteristic oro-facial movements of tardive dyskinesia are at times observed to remit. In patients where parkinsonism and tardive dyskinesia coexist, changes in dyskinetic movements are often reciprocal to the changes in parkinsonism: APK withdrawal may benefit the former and aggravate the latter.

The Pros and Cons of APK Withdrawal

The a foregoing review clearly shows that a considerable number of patients on antipsychotic drugs develop adverse effects from APK withdrawal. On the other hand, a great many patients are apparently totally unaffected by APK withdrawal. Some of these patients may have had pre-withdrawal blood levels below therapeutic range on usual oral doses, as Tune and Coyle demonstrated for Benztropin . It may be assumed that such inter-individual variability in blood level exists for every APK and therefore some patients who show parkinsonism during APK administration (that is, cases of treatment-resistant parkinsonism) are not on therapeutic doses and may not change following APK withdrawal.

The risk-benefit ratio of continuous anti-Parkinson therapy remains a

matter of controversy. Some authors- stress the disadvantages, such as anticholinergic side effects, possible lowering of antipsychotic blood level, and aggravation of tardive dyskinesia. They also note the element of cost and regard prophylactic and maintenance therapy as at best unnecessary and at worst, harmful. Other researchers consider most of these risks of APK therapy to be greatly exaggerated or largely theoretical, while they view the benefits of continuous APK treatment, such as control of subtle extrapyramidal effects and possibly the contribution of a psychotherapeutic effect, as benefits that outweigh the potential hazards.

In the current state of knowledge, it would be considered good clinical practice to attempt to withdraw prophylactic APK after ninety days of administration since acute extrapyramidal symptoms are unlikely to develop beyond this time. Careful attention to withdrawal effects requires periodic follow-up examination of APK withdrawn patients for signs of extrapyramidal disturbance as well as behavioral and mood changes. The optimal technique of APK withdrawal to minimize withdrawal effects is gradual tapering rather than abrupt discontinuation. However, as demonstrated in a recent study, even when gradual APK withdrawal is instituted, about one-third of the patients still appear, after two years, to require APK.

Antidepressants

Withdrawal syndromes from two drug classes used in affective illness appear to be almost nonexistent. Monoamine oxidase inhibitors can be stopped abruptly with no consequences other than a possible reemergence of depressive symptoms within days or weeks. This seems most reasonable since the enzyme inhibition produced by these drugs fades very gradually over a two- or three-week period. There is one recent report describing withdrawal effects from phenelzine in which after one day two patients developed flu-like symptoms lasting for one week.

Lithium also does not cause withdrawal syndromes, a fact supported by one formal study and a large body of informal clinical experience. There are, however, rare occasions in which lithium toxicity may be mistaken for withdrawal. Rosser and Herxheimer reported two cases of nausea and vomiting following chlorpromazine withdrawal in patients who were also on lithium. The differential diagnostic possibilities for the vomiting included: (1) removal of the antiemetic effect of chlorpromazine exposing lithium side effects; (2) risk in serum lithium level brought about by chlorpromazine withdrawal; and (3) chlorpromazine withdrawal effects. Occasionally, a patient will begin to show signs of lithium toxicity that will then worsen for a couple of days after the drug is stopped. The probable mechanism is a rising serum lithium level after drug discontinuation due to dehydration and sodium loss with resulting lithium retention.

Tricyclic antidepressant drugs elicit withdrawal symptoms when dosage is abruptly or rapidly terminated. The literature on withdrawal from antidepressants is rather sparse, however, and deals almost exclusively with imipramine. Kramer and associates studied withdrawal symptoms by means of interviews and nursing notes concerning forty-five patients withdrawn from imipramine after stabilization at dosages of about 300 mg/d. Twenty-two of twenty-six patients treated for over two months experienced clear withdrawal symptoms, while only three of nineteen patients on the medication for less than two months did so. Withdrawal symptoms lasted two weeks or less. Kramer and associates recommended that two to four weeks be allowed for gradually reducing imipramine dosage. They noted that withdrawal symptoms (nausea, vomiting, headache, giddiness, coryza, chills, weakness, fatigue, or muscle pain) responded to a stat dose of 50 mg imipramine followed by more gradual tapering. Shatan described severe withdrawal symptoms in a patient, occurring twenty-four hours after abrupt termination of imipramine (200 mg/d). Symptoms included those noted by Kramer, plus cold sweat, gooseflesh, abdominal cramps, hunger, diarrhea, irritability, insomnia, and restlessness. Symptoms peaked at forty-eight hours and gradually subsided without treatment after a week off medication. Sathananthan and Gershon described three patients who abruptly stopped daily dosages of imipramine of 300 to 450 mg. Within twenty-four hours all three developed anxiety, restlessness, and forced pacing. The syndrome

resembled the akathisia caused by neuroleptics. Again a stat dose of imipramine relieved the symptoms in all three cases within two hours. Andersen and Kristiansen observed withdrawal symptoms in fifteen out of eighty-five patients following both gradual and acute termination of drug treatment with imipramine. Symptoms included sleep disturbances, subjective and objective restlessness and attacks of perspiration, nausea, and vomiting.

Withdrawal symptoms from other tricyclics have also been reported. Gualtieri and Staye described withdrawal symptoms (nausea, vomiting, abdominal cramps, and diarrhea leading to severe dehydration) in an eight-year-old boy who had been on amitriptyline (50 mg/d) for seven months. Kraft found withdrawal symptoms in seven female patients after abrupt discontinuation of clomipramine. These included dizziness, faintness, nausea, feeling "electrically charged," malaise, stomachaches, and anxiety dreams. Two of the patients reported symptoms after placebo substitution. Symptoms tended to be worse after longer term clomipramine therapy. Brown and associates described withdrawal effects in a forty-one-year-old man after twelve years of record dosage of desipramine (1,000 mg/d). During the seventeen-day gradual withdrawal period, only mild symptoms were noted: sore shoulders, insomnia, vivid dreams, and "nerves," all of which faded away without treatment. Other changes during drug withdrawal were an improvement in EEG irregularities and EKG abnormalities and an increase in

delta sleep and REM rebound.

In clinical practice, mild withdrawal symptoms are not uncommon if tricyclics are stopped too rapidly and in the all-too-common situation when a patient runs out of medication. Patients experiencing mild symptoms usually respond well to a dose of the interrupted antidepressant. For instance, Stern and Mendels have reported two cases in which apparent imipramine withdrawal symptoms (nausea, malaise, sweating, salivation, dizziness) came on within twelve hours after the patients failed to take their nightly imipramine dosage, that is thirty-six hours after the last dose. These symptoms were relieved in both cases by resuming imipramine. Withdrawal symptoms probably occur with all tricyclics although not all have been formally studied.

If, similar to phenothiazine withdrawal, tricyclic withdrawal symptoms represent cholinergic rebound due to discontinuation of anticholinergic drugs, desipramine cessation might be less likely to elicit such reactions and newer non-anticholinergic antidepressants, such as mianserin or trazodone, might be free of withdrawal symptoms. Nevertheless, it is a good practice to taper antidepressants slowly, dropping the dose by about one-quarter per week, while watching for withdrawal effects as well as reemergence of the original depression. Shatan makes the argument that tricyclics are “addictive” because they produce withdrawal symptoms and the patient becomes

dependent on them for a feeling of wellbeing. It seems more reasonable to interpret the reemergence of depressive dysphoria as the continued presence of a chronic depression, but the existence of "rebound" depression cannot be ruled out.

Antianxiety Drugs

Abrupt withdrawal of barbiturates in addicts produces a characteristic abstinence syndrome. The time course, symptom characteristics, and outcome were carefully delineated in studies on addict volunteers. Barbiturate-type abstinence phenomena have since been shown to occur with a host of chemically different sedative-hypnotics, such as Glutethimide, ethchlorvynol, paraldehyde, and methaqualone. Meprobamate, the most popular tranquilizer prior to the introduction of the benzodiazepines, has been found to produce marked withdrawal phenomena. Haizlip and Ewing found that forty-four out of forty-seven patients developed insomnia, vomiting, tremors, muscle twitching, anxiety, anorexia, or ataxia on abrupt withdrawal after forty days on high doses of Meprobamate. Eight patients showed hallucinosis and tremors resembling delirium tremens, while three patients developed grand mal seizures. Crawford Little described a case of a thirty-one-year-old nurse who developed a psychotic state with excitement, hostility, and paranoia when coming off 6.4 g/d of Meprobamate. Swanson and Okada reported the death of one patient after withdrawal from very high doses of Meprobamate.

Benzodiazepines have all but replaced the aforementioned compounds as standard tranquilizers and hypnotic agents. Benzodiazepines are more effective and safer, and because of their slower breakdown and elimination than the previously described drugs, they may be less likely to induce severe withdrawal reactions. Nevertheless, there is extensive literature verifying that all degrees of severity of withdrawal symptoms may follow abrupt discontinuation of the use of any benzodiazepine. In this discussion of benzodiazepine withdrawal, the classification offered by Wikler into "minor" and "major" phenomena will be retained.

"Minor" Abstinence Phenomena

Maletzky and Klotter found the following symptom prevalence in twenty-four patients after abrupt diazepam withdrawal: anxiety (95 percent), agitation (75 percent), insomnia (58 percent), tremor (42 percent), diaphoresis (29 percent), pain (25 percent), depression (17 percent), and nightmares (17 percent). Decreased appetite, nausea, muscle twitching, tachycardia, and dizziness have also been observed during diazepam withdrawal. Similar symptoms have been reported from chlordiazepoxide, and from oxazepam.

The time course of the withdrawal reaction has been established by careful daily observation of patients in a hospital setting. Pevnick and

associates observed a thirty-seven-year-old man with a documented daily intake of 30 to 45 mg diazepam over twenty months. Withdrawal was done abruptly under single-blind conditions with placebo substitution. During the first five post-withdrawal days, minimal changes were observed: pulse rate and tremor increased and the patient felt “nervous.” During the fifth night, an abstinence syndrome emerged: there was loss of body weight, increased tremor, twitches, muscle cramps, and facial numbness. The syndrome peaked during the sixth night and seventh day at which time the patient stated that he was “kicking” and requested “Valium.” He became uncooperative and also reported generalized numbness, blurred vision, and decreased appetite for cigarettes. On day eight, the symptoms began to recede and by days nine and ten, he felt “normal.” Body weight returned to normal at day fourteen. A somewhat different course was observed in a thirty-two-year-old man who had taken 15 mg/d diazepam for six years. The first day of placebo substitution was marked by mild symptoms. On the second day, he began to complain of more severe symptoms: anxiety, dizziness, blurred vision, tinnitus, constipation, and palpitations. His condition deteriorated further during the next two days. Re-administration of a single dose of 5 mg diazepam produced a remarkable, almost euphoric effect. The duration of marked abstinence symptoms was fifteen days, followed by gradual improvement. The onset of physiological and emotional distress coincided with the plasma diazepam level dropping to 50 percent of baseline level. Hollister and

associates found chlordiazepoxide withdrawal symptoms appearing mostly between the fourth and seventh days when plasma levels of the drug were 25 and 10 percent of the original levels, respectively. Oxazepam withdrawal symptoms may begin as early as the first day, which is almost certainly due to the faster metabolic breakdown of this compound.

Rebound insomnia is a withdrawal effect peculiar to benzodiazepines with short or intermediate half-lives. Sleep laboratory studies by Kales and associates showed that discontinuation of flunitrazepam, nitrazepam, and triazolam made sleep more difficult, while flurazepam and diazepam, which have longer half-lives, did not.

"Major" Abstinence Reactions

"Major" abstinence reactions include psychotic manifestations and seizures and closely resemble similar syndromes occurring after barbiturate withdrawal. The clinical picture may be dominated by hallucinations, particularly of the visual type, an organic or paranoid psychosis, seizures, hyperthermia, or a gradual progression from minor symptoms to a full-blown toxic psychosis with delirium, paranoid delusions, seizures, and occasionally, Korsakoff's syndrome.

Seizures from diazepam start an average of eight days after abrupt withdrawal, but may occur as early as forty-eight hours. Chlordiazepoxide

withdrawal seizures likewise tend to occur after seven to eight days. Case reports of seizures from lorazepam place the onset at three to five days, corresponding to its faster metabolism. Instances of seizures from clorazepate and oxazepam withdrawal have also been observed. Prolonged coma for up to six hours has been reported as an unusual complication of diazepam withdrawal seizures.

The time course of psychotic syndromes shows great variability. The onset may range from three to fourteen days after withdrawal. If left untreated, the syndrome tends to remit spontaneously in one to two weeks, but treatment is frequently required because of the severity of the condition.

Phenothiazines are generally not helpful and may aggravate the problem by lowering seizure threshold, although occasionally haloperidol or chlorpromazine have been found to be effective. The usual treatment of major abstinence reactions is re treatment with benzodiazepines or the use of pentobarbital or phenobarbital.

The salient features of benzodiazepine withdrawal are summarized in table 18-3.

Clinical Considerations

While the minor withdrawal phenomena are not uncommon, the major

abstinence reactions are exceedingly rare. Marks estimated their incidence to be less than 1 case per 50 million months of therapeutic benzodiazepine use. The risk of seizures and psychoses is proportional to the length of drug exposure and to dosage. However, uncomfortable symptoms have been reported after withdrawal from as little as 15 mg/d diazepam and seizures have been reported after 30 mg/d diazepam, administered for only three months. Previous or concurrent use of other sedative-hypnotics tends to increase the prevalence of withdrawal phenomena,' and in many case reports, the severity of withdrawal reactions was aggravated by the recent or simultaneous withdrawal of other psychotropic drugs or alcohol.

The incidence of withdrawal reactions can be markedly reduced through gradual tapering rather than abrupt withdrawal. When a patient is on several compounds that are cross-tolerant with benzodiazepines, such as sedatives or hypnotics, slow tapering of each compound, one at a time, is likely to minimize the risk of withdrawal effects.

Table 18-3 Benzodiazepine Withdrawal Effects

	MINOR	MAJOR
Common symptoms	Anxiety, insomnia tremor, diaphoresis	Psychosis, delirium hyperthermia, seizures
Onset	1 to 7 days	3 to 12 days
Approximate duration	1 to 10 days	7 to 21 days
Precipitating factors	Abrupt withdrawal, high dosage, prolonged administration, other sedative-hypnotics, alcohol	

Treatment	Retreatment with benzodiazepines is sometimes required	Retreatment with benzodiazepines, pentobarbital, occasionally antipsychotics

Bibliography

Alpert, M. F., Diamond, E. M., and Laski, E. M. "Anticholinergic Exacerbation of Phenothiazine-induced Extrapyramidal Syndrome," *American Journal of Psychiatry,* 133 (1976): 1073-1075.

Andersen, H., and Kristiansen, E. S. "Tofranil Treatment of Endogenous Depressions," *Acta Psychologica et Neurologica Scandinavia,* 34 (1959): 387-397-

Asper, H., et al. "Tolerance Phenomena with Neuroleptics," *European Journal of Pharmacology,* 22 (1973): 287-294.

Ayd, F. J., Jr. "Benzodiazepines: Dependence and Withdrawal," *Journal of the American Medical Association,* 242 (1979): 1401-1402.

Bacopoulos, N. C., et al. "Regional Sensitivity of Primate Brain Dopaminergic Neurons to Haloperidol: Alterations Following Chronic Treatment," *Brain Research,* 157 (1978): 396-401.

Bacopoulos, N. C., et al. "Antipsychotic Drug Action in Schizophrenic Patients: Effect on Cortical Dopamine Metabolism after Long-term Treatment," *Science,* 205 (1979): 1405-1407.

Baldessarini, R. J., et al. "Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association," in press.

Baldessarini, R. J., and Tarsy, D. "Relationship of the Actions of Neuroleptic 20. Drugs to the Pathophysiology of Tardive Dyskinesia," *International Review of Neurobiology,* 21 (1979): 1-45.

Barten, H. H. "Toxic Psychosis with Transient Dysmnestic Syndrome Following Withdrawal from Valium," *American Journal of Psychiatry,* 121 (1965): 1210-1211.

Battegay, R. “Entziehungs Erscheinungen nach abruptem Absetzen von Neuroleptica als Kriterien zu ihrer Differenzierung,” *Nervenarzt,* 37 (1966): 552-556.

Bennett, J. L., and K001, K. H. “Five Phenothiazine Derivatives: Evaluation and Toxicity Studies,” *Archives of General Psychiatry,* 4 (1961): 413-418.

Bourgeois, M., and Bouey, P. “L’antagonisme entre Correcteurs Anti-parkinsoniens et Neuroleptiques. A Propos de Diverses Experiences de Sevrage dont une Personnelle (2 partie),” *Annales de Medico-Psychologie (Paris),* 2 (1976): 699-707.

Bowers, M. B., and Rozitis, A. "Regional Differences in Homovanillic Acid Concentration After Acute and Chronic Administration of Antipsychotic Drugs" *Journal of Pharmacy and Pharmacology,* 26 (1974): 743-745.

----. “Brain Homovanillic Acid: Regional Changes over Time with Antipsychotic Drugs,” *European Journal of Pharmacology,* 39 (1976): 109-115.

Brooks, G. W. “Withdrawal from Neuroleptic Drugs,” *American Journal of Psychiatry,* 115 (1959): 931-932.

Brown, G., et al. “Withdrawal from Long-term High-dose Desipramine Therapy: Clinical and Biological *Changes,” Archives of General Psychiatry,* 35 (1978): 1261-1264.

Burt, D. R., Creese, I., and Snyder, S. H. “Antischizophrenic Drugs: Chronic Treatment Elevates Dopamine Receptor Binding in Brain,” *Science,* 196 (1977): 326-328.

Cahan, R. B., and Parrish, D. D. “Reversibility of Drug-induced Parkinsonism,” *American Journal of Psychiatry,* 116 (1960): 1022-1023.

Chouinard, G., and Jones, B. D. “Neuroleptic-induced Super-sensitivity Psychosis: Clinical and Pharmacologic Characteristics,” *American Journal of Psychiatry,* 137 (1980): 16-21.

----, and Annable, L. “Neuroleptic-induced super-sensitivity Psychosis,” *American Journal of Psychiatry,* 135 (1978): 1409-1410.

Clow, A., et al. “Striatal Dopamine Receptors Become Supersensitive While Rats Are Given

Trifluoperazine for Six Months," *Nature,* 278 (1979): 59-61.

Covi, L., et al. "Length of Treatment with Anxiolytic Sedatives and Response to Their Sudden Withdrawal," Acta Psychiatrica Scandinavia, 49 (1973): 51-64.

Crane, G. E. "Rapid Reversal of Tardive Dyskinesia (ltr to ed.)," *American Journal of Psychiatry*, 130 (1973): 1159.

----. "Tardive Dyskinesia and Drug Research," *Psychopharmacology Bulletin*, 9 (1973): 33.

----, and Naranjo, E. R. "Motor Disorders Induced by Neuroleptics," *Archives of General Psychiatry*, 24 (1971): 179-184.

Crawford Little, J. "A Case of Primary Addiction to Meprobamate," *British Medical Journal Memoranda*, 2 (1963): 794.

Davis, J. M. "Overview: Maintenance Therapy in Psychiatry. I. Schizophrenica," *American Journal of Psychiatry*, 132 (1975): 1237-1245.

Davis, K. L., and Rosenberg, G. S. "Is There A Limbic System Equivalent of Tardive Dyskinesia?", *Biological Psychiatry,* 14 (1979) 699-703.

Davis, K. L., Hollister, L. E., and Fritz, W. C. "Induction of Dopaminergic Mesolimbic Receptor Super-sensitivity by Haloperidol," *Life Sciences*, 23 (1978): 1543-1548.

De Bard, M. L. "Diazepam Withdrawal Syndrome: A Case With Psychosis, Seizure and Coma," *American Journal of Psychiatry*, 136 (1979): 104-105.

Degkwitz, R., and Wenzel, W. "Persistent Extrapyramidal Side Effects After Long-term Application of Neuroleptics," in Brill, H., ed., *Neuropsychopharmacology,* International Congress Series 124, New York: Excerpta Medica Foundation, 1967, pp. 608-615.

Degkwitz, R., et al. "Der zeitliche Zusammenhang zwischen dem Auftreten persistierender extrapyramidaler Hyperkinesen und Psychose-recidiven nach abrupter Unterbrechung langfristiger neuroleptischer Behandlung chronisch schizophrener kranken," *Arzneim Forsch,* 20 (1970): 890-893.

Demars, J. C. A. "Neuromuscular Effects of Long-term Phenothiazine Medication, Electroconvulsive Therapy and Leucotomy," *Journal of Nervous and Mental Disease,* 143 (1966): 73-79.

Di Mascio, A., and Demirgian, E. "Anti-Parkinson Drug Overuse," *Psychosomatics,* 2 (1970): 596-601.

Donlon, P. T., and Blacker, K. H. "Stages of Schizophrenic Decompensation and Reintegration," *Journal of Nervous and Mental Disease,* 157 (1973): 200-209.

Donlon, P. T., and Stenson, R. L. "Neuroleptic Induced Extrapyramidal Symptoms," *Diseases of the Nervous System,* 37 (1976): 629-635.

Dysken, M. W., and Chan, C. H. "Diazepam Withdrawal Psychosis: A Case Report," *American Journal of Psychiatry,* 134 (1977): 153.

Einarson, T. R. "Lorazepam Withdrawal Seizures," *Lancet,* 1 (1980): 151.

Emmelin, N. "Super-sensitivity Following 'Pharmacological Denervation'," *Pharmacological Review,* 13 (1961): 17-37.

Engelhardt, D. M., and Polizos, P. "Adverse Effects of Pharmacotherapy in Childhood Psychosis," in Lipton, M. A., Di Mascio, A., and Killam, K. F., eds., *Psychopharmacology: A Generation of Progress.* New York: Raven Press, 1978, pp. 1463-1469.

Engelhardt, D. M., et al. "Phenothiazines in Prevention of Psychiatric Hospitalization. IV. Delay or Prevention of Hospitalization—A Reevaluation," *Archives of General Psychiatry,* 16 (1967): 98-101.

Escobar, J. I., and Tuason, V. B. "Neuroleptic Withdrawal Dyskinesia," *Psychopharmacology Bulletin,* 15 (1979): 71-74.

Fahn, S., and David, E. "Oral-facial-lingual Dyskinesia Due to Anticholinergic Medication," *Transactions of the American Neurological Association,* 97 (1972): 277-279.

Fann, W. E., and Lake, C. R. "On the Coexistence of Parkinsonism and Tardive Dyskinesia," *Diseases*

of the Nervous System, 35 (1974): 324-326.

Ferholt, J. B., and Stone, W. N. "Severe Delirium After Abrupt Withdrawal of Thiothixene in a Chronic Schizophrenic Patient," *Journal of Nervous and Mental Disease,* 150 (1970): 400-403.

Fink, E. B. "Unexpected and Prolonged Akinesia. A Case Report," *Journal of Clinical Psychiatry,* 39 (1978): 817-818.

Fjalland, B., and Moller-Nielsen, I. "Enchancement of Methylphenidate-induced Stereotypes by Repeated Administration of Neuroleptics," *Psychopharmacologia,* 34 (1974): 105-109.

Fleischhauer, J. "Open Withdrawal of Anti-Parkinson Drugs in The Neuroleptic-induced Parkinson Syndrome," *International Pharmacopsychiatry,* 10 (1975): 222-229.

Floyd, J. B., Jr., and Murphy, C. M. "Hallucinations Following Withdrawal of Valium," *Kentucky Medical Association Journal,* (1976): 549-550.

Forrest, D. V., and Fahn, S. "Tardive Dysphrenia and Subjective Akathisia," (ltr. to editor) *Journal of Clinical Psychiatry,* 40 (1979) 87.

Friend, W. C., et al. "Effect of Haloperidol and Apomorphine Treatment on Dopamine Receptors in Pituitary and Striatum," *American Journal of Psychiatry,* 135 (1978): 839-841.

Fruensgaard, K. "Withdrawal Psychosis: A Study of 30 Consecutive Cases," *Acta Psychiatrica Scandinavia,* 53 (1976): 105-118.

Gallant, D. M., et al. "Withdrawal Symptoms After Abrupt Cessation of Antipsychotic Compounds: Clinical Confirmation in Chronic Schizophrenics," *American Journal of Psychiatry,* 121 (1964): 491-493.

Gardos, G., and Cole, J. O. "Maintenance Antipsychotic Therapy: Is the Cure Worse than the Disease?" *American Journal of Psychiatry,* 133 (1976): 32-36.

----, and Tarsy, D. "Withdrawal Syndromes Associated with Antipsychotic Drugs," *American*

Journal of Psychiatry, 135 (1978): 1321-1324.

Glaubiger, G., and Lefkowitz, R. J. "Elevated Beta-adrenergic Receptor Number After Chronic Propranolol Treatment," *Biochemical Biophysical Res. Communication,* 78 (1977): 720-725.

Goggin, D. A., and Solomon, G. F. "Trihexyphenidyl Abuse for Euphorigenic Effect," *American Journal of Psychiatry,* 13 (1979) 459-460.

Granacher, R. P., and Baldessarini, R. J. "The Usefulness of Physostigmine in Neurology and Psychiatry," in Klawans, H. L., ed., *Clinical Neuropharmacology* vol. New York: Raven Press, 1976, pp. 63-79.

Greenberg, L. M., and Roth, S. "Differential Effects of Abrupt Versus Gradual Withdrawal of Chlorpromazine in Hospitalized Chronic Schizophrenic Patients," *American Journal of Psychiatry,* 123 (1966): 221-226.

Gualtieri, C., and Staye, J. "Withdrawal Symptoms After Abrupt Cessation of Amitriptyline in an Eight-year-old Boy," *American Journal of Psychiatry,* 136 (1979): 457-458.

Haizlip, T. M., and Ewing, J. A. "Meprobamate Habituation. A Controlled Clinical Study", *New England Journal of Medicine,* 258 (1958): 1181-1186.

Hanna, S. M. "A Case of Oxazepam (Serenid D) Dependence," *British Journal of Psychiatry,* 120 (1972): 443-445.

Haskell, D. "Withdrawal of Diazepam," (Ltr. to Editor) *Journal of the American Medical Association,* 233 (1975): 135.

Hershon, H. I., Kennedy, P. F. and McGuire, R. J. "Persistence of Extrapyramidal Disorders and Psychiatric Relapse After Withdrawal of Long-term Phenothiazine Therapy," *British Journal of Psychiatry,* 120 (1972): 41-50.

Hoff, H., and Hoffman, G. "Der Persistierende Extrapyramidale Syndrom bei Neuroleptikatherapie," *Wiener Medizinische Wochenschrift,* 117 (1967): 14-17.

Hogarty, G. E., Goldberg, S. C. and Schooler, N. R. "Drug and Sociotherapy in the Aftercare of Schizophrenic Patients. Two-year relapse rates," *Archives of General Psychiatry,* 31 (1974): 603-608.

Hollister, L. E., Motzenbecker, F. P., and Degan, R. O. "Withdrawal Reactions from Chlordiazepoxide ('Librium')," *Psychopharmacologia,* 2 (1961): 63-68.

Isbell, H., and White, W. M. "Clinical Characteristics of Addictions," *American Journal of Medicine,* 14 (1953): 558-565.

Jackson, D. M., et al. "The Effect of Long-term Penfluridol Treatment on the Sensitivity of the Dopamine Receptors in the Nucleus Accumbens and the Corpus Striatum," *Psychopharmacologia,* 45 (1975): 151-155.

Jacobson, G., Baldessarini, R. J., and Manschrek, T. "Tardive and Withdrawal Dyskinesia Associated with Haloperidol," *American Journal of Psychiatry,* 131 (1974): 993.

Jellinek, T. "Mood Elevating Effect of Trihexyphenidyl and Biperiden in Individuals Taking Antipsychotic Medication," *Diseases of the Nervous System,* 38 (1977): 353-355.

----, Gardos, G. and Cole, J. O. "Adverse Effects of Anti-Parkinson Drug Withdrawal," paper presented at 133rd Annual 85. Meeting of the American Psychiatric Association, San Francisco, Calif., May 5-9, 1980.

Kales, A., et al. "Rebound Insomnia. A Potential Hazard Following Withdrawal of 86. Certain Benzodiazepines," *Journal of the American Medical Association,* 241 (1979): 1692-1695.

Kennedy, P. F. "Chorea and the Phenothiazines," *British Journal of Psychiatry,* 115 (1969): 103-104.

Klawans, H. L., and Rubovits, R. "An Experimental Model of Tardive Dyskinesia," *Journal of Neurological Transmission*, 33 (1972): 235-246.

Klett, C. J., and Caffey, E., Jr. "Evaluating the Long-term Need for Anti-Parkinson Drugs by Chronic Schizophrenics," *Archives of General Psychiatry*, 26 (1972): 374-379.

Kraft, T. B. “Ernstige Abstinentieverschigiselen na het Gebruik van Clomipramine,” Med. T. Geneesk. 121 (1977): 1293.

Kramer J., Klein, D., and Fink, M. “Withdrawal Symptoms Following Discontinuation of Imipramine Therapy,” *American Journal of Psychiatry,* 118 (1961): 549-550.

Kruse, W. “Treatment of Drug-induced Extrapyramidal Symptoms (A Comparative Study of Three Anti-Parkinson Agents),” *Diseases of the Nervous System,* 21 (1960): 79-81.

Kumar, B. B. “Thioridazine, Drug Holidays, and Incidence of Vomiting,” (Letter to the Editor), *Journal of the American Medical Association,* 239 (1978): 25.

Lacoursiere, R. B., Spohn, H. E., and Thompson, K. “Medical Effects of Abrupt Neuroleptic Withdrawal,” *Comprehensive Psychiatry*, 17 (1976): 285-294. 94.

La Polla, A., and Nash, L. R. “Treatment of Phenothiazine-induced Parkinsonism with Biperiden,” *Current Therapeutic Research*, 7 (1961): 536-541.

Lerner, P., et al. “Haloperidol: Effect of Long-term Treatment on Rat Striatal Dopamine Synthesis and Turnover,” *Science*, 197 (1977): 181-183.

Longhren, T. P., Brown, W. A., and Williams, B. W. “Serum Prolactin and Clinical State During Neuroleptic Treatment and Withdrawal,” *American Journal of Psychiatry,* 136 (1979): 108-110.

Luchins, D. J., Freed, W. J., and Wyatt, R. J. “The Role of Cholinergic Super-sensitivity in the Medical Symptoms of Antipsychotic Withdrawal,” *American Journal of Psychiatry,* in press.

McAndrew, J. B., Case, Q., and Treffert, D. A. "Effects of Prolonged Phenothiazine Intake on Psychotic and Other Hospitalized Children" *Journal of Autism and Childhood Schizophrenia,* 2 (1972): 75-91.

McCarthy, J. J. “Tardive Psychosis,” *American Journal of Psychiatry,* (Letter to the Editor), 135 (1978): 625-626.

McLelland, H. A., Blessed, G., and Bhate, S. “Abrupt Withdrawal of Anti-Parkinson in Drugs in

Chronic Schizophrenic Patients," *British Journal of Psychiatry,* 125 (1974): 514-516.

MacVicar, K. "Abuse of Anti-Parkinson Drugs by Psychiatric Patients," *American Journal of Psychiatry,* 134 (1977): 809-811.

Maletzky, B. M., and Klotter, J. "Addiction to Diazepam," *The International Journal of the Addictions,* 11 (1976): 95-115.

Mandel, W., Claffey, B., and Margolis, L. H. "Recurrent Thioperazine-induced Extrapyramidal Reaction Following Placebo Substitution for Maintenance Anti-Parkinson Drug," *American Journal of Psychiatry,* 118 (1961): 351-352.

Mandel, W., and Oliver, W. A. "Withdrawal of Maintenance Anti-Parkinson Drug in the Phenothiazine-induced Extrapyramidal Reaction," *American Journal of Psychiatry,* 118 (1961): 350-351.

Marcotte, D. B. "Neuroleptics and Neurological Reactions," *Southern Medical Journal,* 66 (1973): 321-324.

Marks, J. "The Benzodiazepines," Baltimore: University Park Press, 1978. Marriott, P. "Dependence on Anti-Parkinson in Drugs," *British Medical Journal,* (Letter to the Editor), 1 (1976): 152.

Marriott, P., and Help, A. "Drug Monitoring at an Australian Depot Phenothiazine Clinic," *Journal of Clinical Psychiatry,* 39 (1978): 206-212.

Meltzer, H. Y., and Fang, V. S. "The Effect of Neuroleptics on Serum Prolactin in Schizophrenic Patients," *Archives of General Psychiatry,* 33 (1976): 279-286.

Mendelson, G. "Withdrawal Reactions After Oxazepam," *The Lancet,* (letter to the editor), 11 March, 1978, p. 565.

Miller, R. J., and Hiley, C. R. "Anti-muscarinic Properties of Neuroleptics and Drug-induced Parkinsonism," *Nature,* 248 (1974): 596-597.

Miller, R. R., et al. "Propranolol-withdrawal Rebound Phenomenon," *New England Journal of*

Medicine, 293 (1975): 416-418.

Minter, R., and Murray, G. B. "Diazepam Withdrawal: A Current Problem in Recognition," *Journal of Family Practice,* 7 (1978) 1233-1235.

Moller-Nielsen, I., et al. "Pharmacology of Neuroleptics Upon Repeated Administration," *Psychopharmacologia,* 34 (1974): 95-104.

Morton, M. R. "A Study of the Withdrawal of Chlorpromazine or Trifluoperazine in Chronic Schizophrenia," *American Journal of Psychiatry,* 124 (1968): 143-146.

Muller, P., and Seeman, P. "Brain Neurotransmitter Receptors After Long-term Haloperidol: Dopamine, Acetylcholine, serotonin, 2-noradrenergic and Naloxone Receptors," *Life Sciences,* 21 (1977): 1751-1758.

----. "Dopaminergic Super-sensitivity After Neuroleptics: Time Course and Specificity," *Psychopharmacology,* 60 (1978): 1-11.

Orlov, P., et al. "Withdrawal of Anti-Parkinson Drugs," *Archives of General Psychiatry,* 25 (1971): 410-412.

Pakes, G. E. "Lithium Toxicity with Phenothiazine Withdrawal," *The Lancet,* ii (i979) 701.

Paul, G. L., Tobias, L. L., and Holly, B. L. "Maintenance Psychotropic Drugs in the Presence of Active Treatment Programs," *Archives of General Psychiatry,* 27 (1972): 106-115.

Pecknold, J. C., et al. "Lack of Indication for Use of Anti-Parkinson Medication," *Diseases of the Nervous System,* 32 (1971): 538-541-

Pevnick, J. S., Jasinski, D. R., and Haertzen, C. A. "Abrupt Withdrawal from Therapeutically Administered Diazepam. Report of a Case," *Archives of General Psychiatry,* 35 (1978): 995-998.

Pitt, B. "Withdrawal Symptoms After Stopping Phenelzine?" *British Medical Journal,* 2 (1974): 332-333.

Polizos, P., et al. "Neurological Consequences of Psychotropic Drug Withdrawal in Schizophrenic Children," *Journal of Autism and Childhood Schizophrenia,* 3 (1973): 247-253.

POST, R. M., and Goodwin, F. K. "Time Dependent Effects of Phenothiazines on Dopamine Turnover in Psychiatric Patients," *Science,* 190 (1975): 488-489.

Preskorn, S. J., and Denner, L. J. "Benzodiazepines and Withdrawal Psychosis. Report of Three Cases." *Journal of the American Medical Association,* 237 (1977): 36-38.

Prien, R. F., and Klett, C. J. "An Appraisal of the Long-term Use of Tranquilizing Medication with Hospitalized Chronic Schizophrenics," *Schizophrenia Bulletin,* 5 (1972): 64-73.

Pryce, I. E., and Edwards, H. "Persistent Oral Dyskinesia in Female Mental Hospital Patients," *British Journal of Psychiatry,* 112 (1966): 983-987.

Quitkin, F., et al. "Tardive Dyskinesia: Are First Signs Reversible?" *American Journal of Psychiatry,* 134 (1977): 84-87.

Reimer, F. "Das Absetzungs—Delir," *Nervenarzt,* 36 (1965): 446-447.

Relkin, R. "Death Following Withdrawal of Diazepam," *New York State Journal of Medicine,* 66 (1966), 1770-1772.

Rifkin, A., Klein, D. F., and Quitkin, F. "Withdrawal from Diazepam," *Journal of the American Medical Association,* letter to editor, 238 (1977): 306.

Rifkin, A., et al. "A Study of Abrupt Lithium Withdrawal," *Psychopharmacologia,* (Berl.) 44 (1975): 157-158.

Rifkin, A., et al. "Are Prophylactic Anti-Parkinson Drugs Necessary?" *Archives of General Psychiatry,* 35 (1978), 483-489. Robins, A. H. "Depression in Patients with Parkinsonism," *British Journal of Psychiatry,* 128 (1976): 144-145.

Rosser, R., and Herxheimer, A. "Chlorpromazine, Lithium and Metoclopramide: Unrecognized Synergistic and Antagonistic Effects," *Lancet,* 2 (1979): 97-98.

Roy, P., et al. “Studies with Anti-Parkinsonian Drugs with Chronic Psychiatric Patients,” *International Journal of Neuropsychiatry,* 2 (1966): 65-69.

Rubinstein, J. S. “Abuse of Anti-Parkinson Drugs,” *Journal of the American Medical Association,* 239 (1978): 2365-2366.

Sale, I., and Kristall, H. “Schizophrenia Following Withdrawal from Chronic Phenothiazine Administration: A Case Report,” *Australian and New Zealand Journal of Psychiatry,* 12 (1978): 73-75.

Sathananthan, G., and Gershon, S. “Imipramine Withdrawal: An Akathisia-like Syndrome,” *American Journal of Psychiatry,* 130 (1973): 1286-1287.

Scatton, B. “Differential Regional Development of Tolerance to Increase in Dopamine Turnover Upon Repeated Neuroleptic Administration,” *European Journal of Pharmacology,* 46 (1977): 363-369.

Scatton, B., Glowinski, J., and Joulon, L. “Dopamine Metabolism in the Mesolimbic and Mesocortical Dopaminergic Systems After Single or Repeated Administrations of Neuroleptics,” *Brain Research,* 109 (1976): 184-189.

Selig, J. W., Jr. “A Possible Oxazepam Abstinence Syndrome,” *Journal of the American Medical Association,* 198 (1966): 279-280.

Sellers, E. M. “Clinical Pharmacology and Therapeutics of Benzodiazepines,” *Canadian Medical Association Journal,* 118 (1978): 1533-1538.

Sharpless, S. K. “Reorganization of Function in the Nervous System—Use and Disuse,” *Annual Review of Physiology,* 26 (1964): 357-388.

Shatan, C. “Withdrawal Symptoms After Abrupt Termination of Imipramine,” *Canadian Psychiatric Association Journal,* 11 (suppl.) (1966): 150-158.

Simpson, G. M., and Kunz Bartholini, E. “Relationship of Individual Tolerance, Behavior, and Phenothiazine Produced Extrapyramidal System Disturbance,” *Diseases of the Nervous System,* 29 (1968): 269-274.

Simpson, G. M., Amin, M., and Kunz, E. "Withdrawal Effects of Phenothiazines," *Comprehensive Psychiatry,* 6 (1965): 347-351.

Skirboll, L. R., and Bunney, B. S. "The Effects of Acute and Chronic Haloperidol Treatment on Spontaneously Firing Neurons in the Caudate Nucleus of the Rat," *Life Sciences,* 25 (1979): 1419-1434.

Slater, J. "Suspected Dependence on Chlordiazepoxide Hydrochloride (Librium)," *Canadian Medical Association Journal,* (Letter to editor), 95 (1966): 416-417.

Smith, E. E., and Wesson, D. R. "A New Method for Treatment of Barbiturate Dependence," *Journal of the American Medical Association,* 213 (1970): 294-295.

Snyder, S. H. "Receptors, Neurotransmitters and Drug Responses," *New England Journal of Medicine,* 300 (1979): 465-472.

Snyder, S. H., Greenberg, D., and Yamamura, H. I. "Antischizophrenic Drugs and Brain Cholinergic Receptors," *Archives of General Psychiatry,* 31 (1974): 58-61.

Stern, S., and Mendels, J. "Withdrawal Symptoms During the Course of Imipramine Therapy," *Journal of Clinical Psychiatry,* 41 (1980): 66-69.

Stratas, N. E., et al. "A Study of Drug Induced Parkinsonism," *Diseases of the Nervous System,* 24 (1963): 180.

Swanson, L. A., and Okada, T. "Death After Withdrawal From Meprobamate," *Journal of the American Medical Association,* 184 (1963): 780-781.

Swartzburg, M., Lieb, J., and Schwartz, A. H. "Methaqualone Withdrawal," *Archives of General Psychiatry,* 29 (1973): 46-47.

Tamminga, C. A., et al. "A Neuroendocrine Study of Super-sensitivity in Tardive Dyskinesia," *Archives of General Psychiatry,* 34 (i977) 1199-1203.

Tarsy, D., and Baldessarini, R. J. "Behavioral Super-sensitivity to Apomorphine Following Chronic Treatment with Drugs Which Interfere with the Synaptic Function of

Catecholamines." *Neuropharmacology,* 13 (1974): 927-940.

Thornton, E. W., and Thornton, B. P. "Tardive Dyskinesias from the Major Tranquilizers," *Journal of the Florida Medical Association,* 60 (1973): 24-26.

Trendelenberg, U. "Mechanisms of Super-sensitivity and Sub-sensitivity to Sympathomimetic Amines," *Pharmacology Review,* 18 (1966): 629-640.

Tune, L. E., and Coyle, J. T. "Serum Anti-cholinergics and Extrapyramidal Symptoms," presented at the 132nd Annual Meeting of the American Psychiatric Association, Chicago, 1979.

Tyrer, P. Reply to Einarson, T.R.: "Lorazepam Withdrawal Seizures," *The Lancet,* 1, (1980): 151.

Vyas, I., and Carney, M. W. P. "Diazepam Withdrawal Fits," *British Medical Journal,* 4 (October 1975): 44.

Whittaker, C. B., and Hoy, R. M. "Withdrawal of Perphenazine in Chronic Schizophrenia," *British Journal of Psychiatry,* 109 (1963): 422-427.

Wikler, A. "Diagnosis and Treatment of Drug Dependence of the Barbiturate Type," *American Journal of Psychiatry,* 125 (1968): 758-765.

Winokur, A., et al. "Withdrawal Reaction from Long-term, Low-dosage Administration of Diazepam," *Archives of General Psychiatry,* 37 (1980): 101-105.

Yarbrough, G. G. "Super-sensitivity of Caudate Neurons After Repeated Administration of Haloperidol," *European Journal of Pharmacology,* 31 (1975): 367-369.

Yepes, L. E., and Winsberg, B. G. "Vomiting During Neuroleptic Withdrawal in Children," *American Journal of Psychiatry* 134 (1977): 574.