

Mechanisms and Therapeutic Implications of Neuroleptic Atypicality

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PRECIS

Neuroleptics have proven effective for the overall treatment of schizophrenia. The neuroleptic therapy of schizophrenia, however, has been limited by tardive dyskinesia and by the relative inability of neuroleptics to ameliorate the negative symptoms of schizophrenia. Intensive research has been conducted to identify atypical neuroleptics which would not cause TD and which would have relatively greater efficacy in treating negative symptoms. Based upon animal models of TD and negative symptoms, four neuroleptics have been identified which may have these properties: clozapine, thioridazine, sulpiride, and molindone. Clinical studies of TD suggest that these four potentially atypical agents may have lower dyskinetic potential than typical neuroleptics. Additionally, clinical studies of negative symptoms suggest that molindone and sulpiride, but not clozapine or thioridazine may preferentially treat depressive-like negative schizophrenic symptomatology. The atypical effects of clozapine, thioridazine, sulpiride and molindone, suggest that they may have a distinct place in the pharmacotherapy of schizophrenia.

INTRODUCTION

Since their discovery in the mid-1950s, neuroleptic drugs have proven to be safe and effective treatments for schizophrenia. Schizophrenic subjects treated with neuroleptics have been shown to have improved overall functioning and a decreased need for hospitalization versus non-treated controls. The pharmacotherapy of schizophrenia with neuroleptics, however, has proven to be limited by at least two factors. First, neuroleptics increase the rate at which schizophrenic patients develop the long-term potentially irreversible and incapacitating movement disorder, tardive dyskinesia (TD). Second, neuroleptics have proven relatively ineffective in treating the negative symptoms of schizophrenia (e.g. blunted affect, poverty of speech and of ideation) (1,2) and may induce akinetic symptoms which closely resemble the negative schizophrenic symptoms (3,4). Intensive research has been conducted over the past three decades on both a basic science and a clinical level to determine whether or not these two limitations are inevitable concomitants of neuroleptic therapy. Basic studies using animal models of TD and negative symptoms now suggest that several agents do behave differently from traditional neuroleptics (e.g. chlorpromazine, haloperidol) and may indeed possess atypical clinical properties

including a relatively decreased dyskinesogenic potential and/or a relatively increased efficacy in treating negative symptoms. Four such potentially atypical agents have been identified. Clozapine, a compound of the dibenzodiazepine class, has been the best studied and is considered the prototype atypical neuroleptic. Long-term clinical studies have suggested that clozapine has low to absent dyskinesogenic potential. Clozapine, however, remains available in this country only on an experimental basis because of associated agranulocytosis. Thioridazine, a widely used neuroleptic of the piperidine phenothiazine class, appears to have clozapine-like effects in basic models of TD although to a more limited extent. Detailed clinical studies have not been conducted that would allow a determination of the dyskinesogenic potential of thioridazine. Cases of TD presumably related to thioridazine treatment have been reported and the possible decreased dyskinesogenic potential of thioridazine has been much debated (5,6). Sulpiride, a substituted benzamide, and molindone, an indolic derivative, are other neuroleptics with novel chemical structures. These agents, at least in some dose ranges, behave similarly to clozapine in basic models of TD. While definitive clinical studies have yet to be performed for these agents, studies using masking paradigms suggest that these agents also may have decreased dyskinesogenic potential compared with traditional neuroleptics. Sulpiride and molindone behave differently from traditional neuroleptics in animal models of negative symptoms as well, suggesting that they may also have improved efficacy in treating negative symptoms.

BASIC STUDIES

The role of dopaminergic hyperactivity in schizophrenic pathophysiology has now been well established. Agents which increase brain dopaminergic transmission worsen overall schizophrenic symptomatology. The potency with which neuroleptic agents ameliorate schizophrenic symptoms correlates with their potency in blocking dopaminergic transmission at D_2 type dopamine receptors (7,8). Less well established, however, is the role of the various brain dopaminergic systems in contributing to schizophrenic pathophysiology and the clinical response to neuroleptics. Three separate dopaminergic systems have been identified in forebrain. Two of these, the mesocortical and mesolimbic systems arise from the midbrain ventral tegmental area (area A10) and innervate the neocortex (e.g. frontal cortex, cingulate cortex) and limbic system (e.g. nucleus accumbens) respectively. The third arises from the substantia nigra (area A9) and innervates the neostriatum. The mesocortical and mesolimbic systems are thought to subserve cognition and affective regulation while the nigrostriatal system, which has been implicated in the pathophysiology of Parkinson's disease (9) and Huntington's chorea (10), is thought to be involved mainly with regulation of brain motoric systems. The therapeutic actions of neuroleptics and their behavioral side effects may result primarily from their actions in the mesolimbic and mesocortical systems while the dyskinesogenic

effects of neuroleptics are likely to be mediated by their actions on the nigrostriatal system (7,8). As a result, agents which selectively spare the nigrostriatal system should have a relatively decreased risk of inducing TD. Several model systems have been used in an attempt to measure the effects of neuroleptics on the mesocortical and mesolimbic systems versus their effects on the nigrostriatal system. Three of these paradigms in particular have gained widespread acceptance (Table 1). Studies using these paradigms suggest that the proposed atypical agents clozapine, thioridazine, sulpiride, and molindone induce less inhibition of nigrostriatal dopaminergic transmission than traditional agents. These agents, therefore, might have a relatively decreased risk for inducing motoric side effects and, in particular, TD.

Behavioral Supersensitivity

The first model of TD is based upon the observation that in rats the dopaminergic agent amphetamine produces a characteristic syndrome of stereotypies and hyperactivity. Amphetamine-induced stereotypies have been shown to be mediated by the nigrostriatal system while amphetamine-induced hyperactivity is mediated by the mesolimbic system (11,12). Typical neuroleptic agents

TABLE 1.

Summary of Animal Models for Tardive Dyskinesia

Paradigm		Typical Neuroleptics	Atypical Neuroleptics
Behavioral supersensitivity	acute:	↓ amphetamine induced hyperactivity ↓ amphetamine induced stereotypy	↓ amphetamine induced hyperactivity N.C. amphetamine induced stereotypy
	chronic:	↑ amphetamine induced stereotypy ↑ amphetamine induced stereotypy	↑ amphetamine induced stereotypy N.C. amphetamine induced stereotypy
Receptor supersensitivity	chronic:	↑ receptor density - nucleus accumbens ↑ receptor density - striatum	↑ receptor density - nucleus accumbens N.C. receptor density striatum
Depolarization inactivation	acute:	↑ firing rate - A9 ↑ firing rate - A10	N.C. or ↓ firing rate - A9 ↑ firing rate - A10
	chronic:	↓ firing rate - A9 ↓ firing rate - A10	N.C. firing rate - A9 ↓ firing rate - A10

Effects of acute and chronic treatments with typical and atypical neuroleptics on amphetamine-induced hyperactivity and stereotypies, on dopamine receptor density in nucleus accumbens and striatum and on the firing rate of neurons in A9 and A10 midbrain dopaminergic nuclei. N.C. indicates no change.

acutely block both amphetamine-induced stereotypies and hyperactivity suggesting that they induce a net dopaminergic blockade in both the nigrostriatal and the mesolimbic systems. The prototypical atypical agent clozapine, conversely, inhibits only amphetamine-induced hyperactivity while paradoxically enhancing amphetamine-induced stereotypies (13–17). Clozapine, therefore, appears to block dopaminergic transmission only in the mesolimbic system while sparing or possibly enhancing nigrostriatal dopaminergic transmission. Thioridazine (16–18), sulpiride (13,16,17,19–21) and molindone (22) also potentiate amphetamine-induced stereotypies suggesting that these agents also spare nigrostriatal system functioning.

Following chronic treatment with typical neuroleptic agents, rats show an increased sensitivity for developing amphetamine-induced stereotypies and hyperactivity. This increased sensitivity is thought to result from a compensatory supersensitivity of nigrostriatal and mesolimbic dopaminergic receptors following prolonged blockade. In contrast to typical agents, clozapine has been shown to induce supersensitivity only of amphetamine-induced hyperactivity and not of amphetamine-induced stereotypies (14,15) suggesting that it does not induce long-term changes in nigrostriatal system functioning. Thioridazine (23), sulpiride (19) and molindone (24,25) either do not induce supersensitivity to amphetamine-induced stereotypies in rats following chronic treatment or do so with considerably less potency than equivalent dosages of traditional agents. While a relationship between behavioral supersensitivity to amphetamine and TD has yet to be demonstrated, the relative ability of these proposed atypical agents to spare the nigrostriatal system suggests that these agents may be less likely than typical agents to induce long-term changes in the nigrostriatal system.

Receptor Supersensitivity

In order to investigate whether dopamine receptor supersensitivity underlies the neuroleptic-induced behavioral supersensitivity, dopamine receptors in the striatum and nucleus accumbens have been studied directly using radiolabelled agents which bind specifically to D₂-type dopamine receptors (e.g. [³H]spiperone). Traditional neuroleptics have been shown to induce an increase in the number of D₂ receptors in the striatum following days to weeks of continuous treatment. By contrast clozapine (14,15,26), sulpiride (26,27) and molindone (24) do not induce supersensitivity of striatal D₂ receptors, suggesting again that these agents affect nigrostriatal dopaminergic transmission to a lesser extent than traditional agents do.

Shortly after the discovery of neuroleptic-induced supersensitivity of striatal D₂ receptors it was proposed that dyskinetic movements result from the interaction of endogenous dopamine with the supersensitive D₂ receptors (28,29). Recent findings, however, have called this theory into question (30). First, receptor supersensitivity can develop after a single administration of

neuroleptics whereas dyskinetic symptoms arise only after prolonged administration. Second, receptor supersensitivity develops in all subjects tested, while TD develops sporadically. Third, receptor supersensitivity remains reversible upon withdrawal of neuroleptics while TD may persist indefinitely. Finally, detailed post-mortem studies have failed to find an association between striatal D_2 receptor density and a prior history of TD (31). D_2 receptor supersensitivity, therefore, is probably not mechanistically related to TD. Receptor supersensitivity may however be seen as a step in the cascade of events which ultimately results in the expression of dyskinetic symptoms.

Depolarization Inactivation

In addition to their behavioral and biochemical effects, neuroleptics have been shown to directly affect the firing patterns of dopaminergic neurons in the A9 and A10 midbrain nuclei, which originate in the nigrostriatal and mesolimbic/mesocortical pathways respectively. Blockade of dopaminergic transmission depolarizes neurons in both the A9 and A10 nuclei, leading to an acute increase in their firing rate (32). Following chronic neuroleptic-induced depolarization, however, these neurons gradually lose their coordinated pattern of firing and over time become completely quiescent. Direct administration of γ -aminobutyric acid (GABA), an inhibitory transmitter, can restore activity to these inactivated neurons suggesting that their inactivation is due to chronic depolarization (33). Neuroleptic-induced depolarization of A10 neurons is thought to underlie the antipsychotic effects of neuroleptics and possibly their behavioral side effects while depolarization inactivation of A9 neurons may be the first step in a sequence of events leading to TD (34). In this theory (35), it is hypothesized that blockade of postsynaptic striatal dopamine receptors leads to a decrease in the activity of the normally inhibitory GABA-mediated striatonigral feedback pathway which leads to a depolarization of A9 neurons and an acute increase of striatal dopamine release. Following prolonged dopaminergic blockade, however, the A9 neurons become incapable of sustaining the increased firing rate and become gradually inactive leading to a decline in striatal dopamine release. As long as the striatonigral GABAergic neurons remain intact, the process remains reversible. Dopaminergic denervation of the GABAergic neurons, however, appears to place an adaptive stress upon them which over time may facilitate their degeneration. Degeneration of GABAergic striatonigral neurons has been implicated in the pathophysiology of Huntington's chorea (10) and Wilson's disease, conditions which present with dyskinetic symptoms clinically indistinguishable from those of TD, and so may be the final common pathway for the generation of dyskinetic movements. Experimental destruction of the striatonigral pathway in animals leads to depolarization inactivation in A9 and to the development of dyskinetic movements (36). *Cebus* monkeys who are exposed to neuroleptics over a period of years can develop dyskinesias which closely resemble those of TD (37). Monkeys who develop dyskinesias have been shown

to have significantly lower levels of GABA in the substantia nigra than monkeys who do not (38) suggesting that a failure of GABAergic neurons to adapt to functional dopaminergic denervation may be etiologically related to the development of dyskinesias. Human post-mortem studies of schizophrenics have likewise demonstrated a decreased striatal GABA level in subjects with a prior history of TD versus those without (31). No differences in dopamine receptor numbers were found in these patients. These findings suggest that while depolarization inactivation of A9 neurons does not directly underlie dyskinetic movements. It may be the first of a cascade of events which ultimately results in TD. Agents which do not induce depolarization inactivation of A9 neurons, therefore, should be relatively without dyskinetogenic potential.

Administration of the traditional neuroleptics chlorpromazine, haloperidol and fluphenazine has been shown to lead to an acute increase in the firing rate of neurons in both A9 and A10 followed by a sustained depolarization inactivation of these neurons (39-41). By contrast, clozapine (33,39,40), thioridazine (39), sulpiride (39) and molindone (39) have been shown not to induce depolarization inactivation in A9. Acute administration of these agents increases the firing rate of neurons in A10 but not in A9 while their chronic administration leads to a decrease in the firing rates of neurons only in A10. Clozapine and molindone (41) have also been shown to reverse the inhibition of firing rates induced by chronic haloperidol at the dosages used in these studies. Clozapine, thioridazine, sulpiride and molindone therefore, appear not to inhibit nigrostriatal dopaminergic transmission and so may be less likely than traditional agents to induce TD. l-Sulpiride, the "active" isomer of sulpiride, has been shown to induce depolarization inactivation of A9 when administered on its own whereas d-sulpiride, the "inactive" isomer, has no effect (33). For sulpiride, therefore, atypicality may depend upon administering racemate l-sulpiride which is the clinically available form of the drug.

Possible Mechanisms of Neuroleptic Atypicality

The exact mechanism by which atypical neuroleptics spare the nigrostriatal system remains a question of intense debate. One common ability of all putative atypicals is to selectively increase presynaptic dopamine release in the striatum. Presynaptic dopamine synthesis and release can be assayed either by measuring the activity of tyrosine hydroxylase, the rate limiting enzyme responsible for dopamine synthesis, or by directly measuring the levels of dopamine metabolites. Using these assays, it has been found that clozapine, thioridazine, sulpiride and molindone all increase dopamine synthesis and release in the striatum but that they differ in the mechanism by which they do so. Clozapine and thioridazine have been found to stimulate tyrosine hydroxylase activity via non-haloperidol sensitive receptors (43) and to increase DA metabolite levels via a transsynaptic mechanism (44). Molindone (44) and sulpiride (45), conversely, appear to operate via a homosynaptic mechanism. The atypical effects of

clozapine and thioridazine, therefore, are probably mediated via their actions on the non-dopaminergic brain systems which regulate dopaminergic transmission while the atypical effects of molindone and sulpiride are most probably mediated via their direct effects on the dopaminergic terminals.

Clozapine and to a lesser extent thioridazine have been shown to have relatively low potencies of action at brain D₂ receptors and relatively high potencies at D₁ dopaminergic receptors, at adrenergic receptors, at muscarinic cholinergic receptors and at serotonergic receptors (46,47). It remains unclear which if any of these receptors mediates the atypical effects of clozapine and thioridazine. Most attention has been focused upon anti-cholinergic and anti-adrenergic effects (48,49). More recently it has been suggested that the anti-seritonergetic potency of clozapine may contribute to its atypicality as well. In one study, LSD, a serotonergic agonist, potentiated the hyperactivity induced by the dopaminergic agent apomorphine. Clozapine but not haloperidol or sulpiride inhibited the LSD-induced potentiation of apomorphine hyperactivity (50) suggesting that clozapine has a distinct effect on brain serotonergic systems when compared with other neuroleptics. Thioridazine was not explicitly tested in this paradigm. Striatum (51) and substantia nigra (32) receive innervation from brain serotonergic systems suggesting that serotonin may play a modulatory role in nigrostriatal system functioning. The mechanism by which clozapine's anti-serotonergic effects might result in a decreased dyskinetic potential, however, remains to be determined.

By contrast to clozapine and thioridazine, molindone and sulpiride bind extremely weakly to D₁ receptors, to muscarinic cholinergic receptors, to adrenergic receptors and to serotonergic receptors (46,47). Both molindone and sulpiride, however, bind potently to a class of dopamine receptors called dopamine autoreceptors (DARs). DARs respond directly to pre-synaptically released dopamine and serve to inhibit further dopamine release. Blockade of this negative feedback system effectively increases the rate of pre-synaptic dopamine synthesis and release (52). Low dose apomorphine (<0.4 mg/kg) selectively stimulates DARs (53). Using apomorphine to assess DAR functioning, it has been found that molindone inhibits DARs 2-4 times more potently than post-synaptic receptors. In the dose range of 1-3 mg/kg, molindone preferentially inhibits DARs (22,54-56). Sulpiride has also been shown to preferentially inhibit DARs, at doses up to 10 mg/kg (21,53). Clozapine and thioridazine, as opposed to molindone and sulpiride, appear to antagonize DAR-mediated activities extremely weakly (53,54). DARs have been shown to regulate dopamine release in the nigrostriatal system (59). Agents which act preferentially on DARs, therefore, would be expected not to inhibit and possibly to enhance dopaminergic neurotransmission in the striatum. Such an effect could underlie the atypical effects of molindone and sulpiride in animal models of TD. It should be noted, however, that at high doses molindone and sulpiride can effectively block postsynaptic dopamine receptors. At high doses, therefore, these agents might be expected to behave similarly to traditional neuroleptics.

A Model for Negative Symptoms

In addition to regulating nigrostriatal functioning, DARs regulate mesolimbic dopaminergic transmission (52,60,61). Stimulation of postsynaptic dopamine receptors with amphetamine or high dose apomorphine has been shown to induce motor hyperactivity which is mediated via the mesolimbic system. Low dose apomorphine, conversely, binds preferentially to DARs, leading to decreased mesolimbic dopamine release and a characteristic syndrome of hypomotility and sedation in rodents (53). Neither clozapine nor thioridazine reverses the hypomotility induced by low dose apomorphine (53). These agents, therefore, appear to have little ability to reverse mesolimbic dopaminergic blockade. Conversely sulpiride has been shown to inhibit apomorphine-induced hypomotility (53) suggesting that it may not induce net dopaminergic underactivity in the mesolimbic system when administered alone. While the effect of molindone on hypomotility has not been explicitly tested, molindone has been shown to inhibit the effects of low dose apomorphine on dopamine release (54,56) and so would be expected to share sulpiride's behavioral effects.

The relationship between apomorphine-induced hypomotility and schizophrenic symptomatology remains to be determined. In one study (62), however, it was shown that apomorphine-induced hypomotility is accompanied by a reward deficit in rats. Untreated rats show an ability to increase their rate of bar pressing when they are shifted from a schedule in which they are rewarded with a food pellet for each response to one in which they are rewarded for only every fourth response. After three sessions untreated rats are able to obtain the same number of pellets as before the shift in reward schedule. Rats pretreated with low dose apomorphine, however, fail to significantly alter their rate of responding following the shift in reward schedule. Since the rats remain physically capable of increasing their responding rate, this failure of responding may represent a decreased responsiveness to secondary reinforcers. It was proposed that this decreased responsiveness might represent a model for depressive-like negative schizophrenic symptoms such as anhedonia and emotional withdrawal. Sulpiride completely reverses the reward deficit induced by apomorphine. Thioridazine, haloperidol, chlorpromazine and fluphenazine by contrast fail to reverse the apomorphine-induced reward deficit at any dose. Molindone has not been explicitly tested in this paradigm.

In man, the mesolimbic system appears to regulate behavioral activity and mood. Low dose apomorphine produces sedation and sleep and may precipitate severe depression (63). Underactivity of the mesolimbic system appears to be involved in the psychomotor retardation and poor environmental reactivity seen in patients with Parkinson's disease (9) and endogenous depression (64,65). Furthermore, based upon animal models, it has been postulated that DAR-hypersensitivity, leading to diminished mesolimbic dopamine release, might be etiologic in some forms of retarded depression (66). The role of DARs in humans, therefore, may be similar to their role in rodents. The ability of

molindone and sulpiride to preferentially block DARs might predict that these agents could preferentially treat the depressive-like negative symptoms including psychomotor retardation and emotional withdrawal.

CLINICAL STUDIES

While the basic models of TD and negative symptoms suggest that clozapine, thioridazine, sulpiride and molindone may produce atypical clinical effects, ultimate confirmation or refutation of these predictions can only be obtained from detailed clinical studies. Since TD generally develops 1–2 years after the initiation of neuroleptic therapy and occurs only in a minority of subjects (66), definitive comparison of the relative dyskinesogenic potential of neuroleptics requires long-term longitudinal studies of first break schizophrenic patients spanning several years and involving large numbers of subjects. Of the four neuroleptics which show atypical effects in animal models, only clozapine has been subjected to sufficient study to suggest that it has significantly lower dyskinesogenic potential than traditional agents. In one study of 216 psychiatric patients treated with clozapine as sole neuroleptic for up to 12 years no cases of TD were reported (67). Other studies have similarly shown a decreased dyskinesogenic potential for clozapine (68). Thioridazine, sulpiride and molindone, by contrast, have not been subjected to sufficiently long-term studies to allow an estimation of their dyskinesogenic potential versus traditional agents.

In the absence of long-term longitudinal studies of schizophrenic patients, "masking" paradigms have been used to try to study the relative dyskinesogenic potentials of neuroleptic agents. In this approach, subjects are chosen who have developed persistent withdrawal exacerbated TD. These subjects are assigned to different neuroleptic regimens and the potency with which these agents mask dyskinesic symptoms is determined. Based upon animal studies (37,69,70), it has been proposed that those agents which are least potent in masking dyskinesic symptoms should be least likely to induce *de novo* TD. In a closely related paradigm, subjects with preexisting TD are exposed to neuroleptics and the post- *vs.* pre-exposure severity of TD is determined. Studies using these paradigms have been conducted with haloperidol and with the proposed atypicals clozapine, thioridazine and molindone. Active treatment with haloperidol has been shown to potently mask dyskinesic symptoms. Subsequent withdrawal of haloperidol leads to a rebound worsening of dyskinesic symptoms suggesting that a progression of the underlying process has occurred (69–76). Clozapine, by contrast, has been shown to have no significant antidyskinesic effects and withdrawal of clozapine does not lead to rebound worsening (70,71). Thioridazine (70) and molindone (72) also mask dyskinesic symptoms less potently than haloperidol does. These agents, however, do produce a significant degree of masking and therefore cannot be considered free of dyskinesogenic potential. While sulpiride has been shown in humans to have some ability to mask dyskinesic symptoms (73,74), its potency has not been directly compared

either to traditional neuroleptics or to other atypicals. In *Cebus* monkeys with persistent neuroleptic-induced orofacial dyskinesias sulpiride has been shown to mask dyskinetic movements to a lesser degree than either haloperidol or fluphenazine (75). In addition to clozapine, thioridazine (70) and sulpiride (75) do not induce rebound worsening of TD. Additionally, clozapine and thioridazine have also been found not to induce rebound worsening in *Cebus* monkeys with persistent dyskinesias (76). Molindone has not been directly tested in the rebound worsening paradigm. These studies support the basic prediction that clozapine, thioridazine, sulpiride and molindone have relatively decreased dyskinetogenic potential when compared with traditional agents. Only clozapine, however, appears inactive in these paradigms, suggesting that the other three agents might still have significant although decreased risks of associated TD. Furthermore, although thioridazine does not produce rebound worsening of TD in monkeys, two of its metabolites, mesoridazine and sulforidazine, have been shown to induce rebound worsening while a third metabolite, thioridazine ring sulfoxide, does not (69). Individual metabolism may therefore affect whether thioridazine and possibly other neuroleptics have decreased dyskinetogenic potential in any given subject.

Negative symptoms have also proven difficult to study clinically. No definitive studies have been conducted which either support or refute the suggestion that sulpiride and molindone should be more efficacious than other neuroleptics in treating negative symptoms. Difficulties arise because negative symptoms have proven difficult both to define and operationalize. In the last few years, however, phenomenological studies have demonstrated that depressive-like negative symptoms (e.g. fatigue, blunted affect and loss of interest) constitute a cluster of symptoms which are distinct from either positive or hebephrenic-like negative symptoms (77,78). The separate clustering of these symptoms suggests that they may be etiologically distinct from other symptoms of schizophrenia and may possibly be mediated by different brain pathways. Operationalized criteria for negative symptoms have been proposed only within the last few years (79,80). Since no studies have directly compared neuroleptics using well validated negative symptom scales, no firm conclusions can be drawn concerning the relative effectiveness of typical and atypical neuroleptics in treating negative symptoms. Preliminary conclusions can be drawn, however, from medication trials which utilized the Brief Psychiatric Rating Scale (BPRS) (81). Three BPRS items, emotional withdrawal, blunted affect, and motor retardation have been found to correlate with negative symptoms scores but not with positive symptoms suggesting that they might be useful post-hoc measures of negative symptomatology (77,82). These symptoms are commonly combined to form the withdrawal/retardation subscale (81).

In reviewing three studies (83–85) which compared clozapine either to baseline or to reference neuroleptic (chlorpromazine or haloperidol), clozapine significantly improved symptoms of withdrawal and retardation in two of the three. In none of these studies, however, were the differences significant versus

a reference neuroleptic. In a fourth study, clozapine failed to improve any of the BPRS negative symptoms (86). Perhaps most indicative of the effects of clozapine are the results of a large multicenter European study (87) in which clozapine was compared with three reference neuroleptics. While clozapine was effective overall in treating BPRS negative symptoms, no clear differential effect was observed. In one substudy, clozapine was superior to chlorpromazine in the treatment of withdrawal/retardation. The differential effect, however, was less than for hyperactivity and core symptoms, however, suggesting that clozapine's superiority was global rather than restricted to negative symptoms.

Thioridazine and its active metabolite mesoridazine have similarly been compared with reference neuroleptics in a number of studies. In three studies (88–90), thioridazine has been shown to be relatively ineffective in ameliorating emotional withdrawal and psychomotor retardation. Mesoridazine, its active metabolite, has been shown to be somewhat more effective in the treatment of negative symptoms (89–93) possibly because it is less sedating. Mesoridazine also, however, has been found not to be significantly better than reference in treating negative symptoms. Moreover, in one study in which all BPRS symptoms improved significantly following treatment with mesoridazine, blunted affect and emotional withdrawal showed the least improvement (93).

Sulpiride has been relatively poorly studied in trials which employ the BPRS. In three such studies (94–96), sulpiride was found to consistently ameliorate emotional withdrawal, motor retardation and emotional blunting along with the subscale anergia, although in none of these studies was sulpiride significantly superior to the reference neuroleptic (haloperidol). However, in one study which used the Comprehensive Psychopathological Rating Scale (CPRS) to compare sulpiride versus chlorpromazine (97), sulpiride was found to be significantly superior to chlorpromazine in the treatment of autistic symptoms. These symptoms which consisted of inability to feel, lassitude, withdrawal, reduced speech and slowness of movement are analogous to BPRS defined negative symptoms but have not been directly validated against them. While sulpiride and chlorpromazine both produced significant improvement in global symptomatology and in positive symptoms, sulpiride significantly decreased autistic symptoms whereas chlorpromazine did not. Of interest, sulpiride-induced improvement in negative symptoms was found to be inversely correlated with sulpiride drug concentration such that those subjects with the highest serum sulpiride concentrations were found to have the least improvement in negative symptoms. Moreover, no significant correlation was found between serum levels of either sulpiride (or chlorpromazine) and positive schizophrenic symptoms. Since the dosage of sulpiride used in the last study (800 mg/day) was significantly less than the dosages in the three studies employing the BPRS (1200–1600 mg/d mean final dosage) the differences in outcome might be related to the dosage differences. Two other uncontrolled studies have also suggested that sulpiride may have anti-autistic effects at dosages of 800 (98) and 600–1200 (99) mg/day. These studies, therefore, suggest that low dose

sulpiride may have relatively improved efficacy in treating negative symptoms although at high doses this differential effect may be lost.

Of 16 clinical trials with molindone, 7 have compared it to a reference neuroleptic using the BPRS (100-106). Of these, six demonstrated improvement either in the items; emotional withdrawal, motor retardation and blunted affect or in the withdrawal/retardation subscale which encompasses these items. Of the four studies which measured the withdrawal/retardation subscale explicitly (103-106), all four demonstrated a significant response of these symptoms to molindone but not to reference neuroleptic. In three of these studies, the preferential effects of molindone on negative symptoms were statistically significant. These studies support the prediction based upon animal models that molindone may be superior to traditional neuroleptics in the treatment of negative symptoms.

THERAPEUTIC IMPLICATIONS

These clinical studies support the animal model-based predictions that clozapine, thioridazine, molindone, and sulpiride may have relatively decreased dyskinetogenic potential compared with traditional agents. Only clozapine, however, appears completely free of associated TD. Of the four atypical agents, only two, thioridazine and molindone, are currently available for non-experimental use in the U.S. These agents appear to differ in the mechanism of their atypicality and in their clinical effects. Thioridazine which is a relatively sedating neuroleptic with no apparent specific efficacy in treating negative symptoms appears to be more clozapine-like in its mechanism of atypicality. Molindone, conversely, more closely resembles the proposed atypical agent sulpiride and appears to produce atypical clinical effects by virtue of its ability to selectively block presynaptic dopamine autoreceptors (DARs). Molindone, like sulpiride, has been shown to be relatively more effective in treating negative symptoms of schizophrenia than traditional neuroleptics. A theoretical concern with molindone is that, like sulpiride, it may lose its atypicality at high dosages. In animal studies, molindone has been shown to lose some degree of atypicality at dosages over 3 mg/kg (24,25). Whether a similar therapeutic window exists clinically remains to be determined.

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