Pharmacotherapy of Stereotypic Movement Disorders

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Although few studies have focused on the pharmacotherapy of stereotypic movement disorder (SMD) per se, there is a larger literature on the pharmacotherapy of stereotypic behaviors. In the earlier paper on the phenomenology of SMD in this issue (pp 307-312), it was noted that a number of disorders (eg, autism, trichotillomania) are characterized by stereotypic symptoms. Rather than reviewing the pharmacotherapy of each of these disorders here, we focus on agents that may be effective when SMD or stereotypic behavior is the target symptom.

Several different classes of medication may be valuable in the pharmacotherapy of SMD or stereotypic symptoms. For many years, antipsychotics have been used to decrease stereotypic symptoms in patients with mental retardation. More recently, antidepressants, particularly serotonin reuptake inhibitors, have become increasingly used in this context. We will therefore focus on these two classes of medication in particular.

Dopaminergic Agents

Typical antipsychotics have long been used to manage stereotyped symptoms, including self-injurious stereotypies in mental retardation. Many reports have indicated that these agents can have significant therapeutic effects; for example, in an open trial, fluphenazine (2-8 mg/day) led to clinical improvement in stereotypic self-injury in 11 of 15 patients with mental retardation. Conversely, few rigorous controlled studies have been undertaken in this population, and taken together with the possibility of important adverse effects (such as oversedation and tardive dyskinesia), long-term use of these agents has been questioned repeatedly. Antipsychotics may also be considered in several disorders characterized specifically by mental retardation and stereotypic or self-injurious behaviors. The dopamine system has, for example, been implicated in the mediation of self-injurious behaviors in Lesch-Nyan syndrome (LNS), and dopamine blockers have been used for their treatment. Unfortunately, long-term treatment with these agents is not clearly of benefit in LNS.

Preliminary evidence suggests that atypical antipsychotics, such as clozapine, which are both dopamine blockers and 5HT2 antagonists, may also be useful in reducing stereotypic behaviors and other target symptoms in patients with mental retardation. Given the apparently favorable side effect profile of many of the newer agents, such as risperidone, controlled and long-term trials with these agents are clearly warranted.

Controlled trials have also demonstrated that typical antipsychotics such as haloperidol are effective in about 50% of patients with autism for target symptoms including stereotypic and self-injurious behaviors. Clinical experience indicates that where a medication is ineffective in autism, an agent from a different class may be useful.
chotics may also ultimately prove useful in this disorder.17 Interestingly, dopamine agonists may also have a role in certain pervasive developmental disorders.18 Although they do not strictly speaking fall under the rubric of SMD, tics, obsessions and compulsions, and hair-pulling may also respond to treatment with antipsychotics. Typical antipsychotics such as haloperidol and pimozide have long proven the mainstay treatment of tics and other behavioral disturbances19 that characterize Tourette's disorder, and newer atypical agents such as risperidone also show promise.20

In obsessive-compulsive disorder (OCD), augmentation of serotonin reuptake inhibitors (SRIs) with haloperidol may be particularly helpful in patients with comorbid tics,21 and preliminary studies of risperidone augmentation again appear promising.22 This augmentation strategy may also be useful in trichotillomania.23,24 Nevertheless, concerns about the safety of such combinations should also be borne in mind.25-27

In summary, although typical antipsychotics do appear to decrease stereotypic symptoms in various disorders, concerns about efficacy and safety raise significant cautions. Nevertheless, these agents may be a useful option in the treatment of certain conditions, particularly in the absence of alternative effective interventions. Furthermore, the introduction of the atypical antipsychotics provides clinicians with a generally safer class of medications that deserves further controlled study in patients with stereotypic movement disorder.

SEROTONERGIC AGENTS

Serotonin Reuptake Inhibitors

A recent retrospective review of antidepressants in patients with mental retardation suggested that response of self-injurious stereotypies was higher for SRIs and was not predicted by co-morbid depressive symptoms.28 Indeed, both open29-32 and controlled33,34 studies have confirmed the efficacy of SRIs in the treatment of stereotypic symptoms and self-injurious stereotypies in patients with mental retardation. There is, however, a lack of prospective controlled trials comparing SRIs and other antidepressants in this patient population.

The SRIs may also be useful in certain specific syndromes characterized by mental retardation and stereotypic symptoms. For example, fluoxetine has been described as useful for self-injurious stereotypies in a number of cases of Prader-Willi Syndrome (PWS).36 Furthermore, a survey of caretakers of patients with PWS suggested that the serotonin reuptake inhibitors may be helpful for both impulsive-aggressive and "compulsive" symptoms (such as stereotypic skin-picking) in some patients.37

Relatively little work has been undertaken on the pharmacotherapy of stereotypic movement disorder in intellectually normal adults. In their pioneering study, Castellanos and colleagues38 compared clomipramine, predominantly an SRI, and desipramine, a predominantly noradrenergic reuptake inhibitor, in a cross-over trial. Although clomipramine appeared promising in a number of cases, too few patients completed the trial to demonstrate a clear benefit of clomipramine over desipramine.

Nevertheless, several case reports suggest that SRIs may be useful in patients with skin picking, head banging, and other stereotypic behaviors.39-42 In a series of 30 patients with skin-picking, an open trial of sertraline demonstrated efficacy.42 A retrospective treatment review of body dysmorphic disorder patients with skin-picking indicated that SRIs were often effective, whereas other agents were not. Finally, in their controlled study, Simeon and colleagues43 found that fluoxetine (20mg daily) for 8 weeks was significantly superior to placebo in decreasing compulsive skin picking in intellectually normal patients.

Although Castellanos and colleagues39 were unable to show clear benefit of clomipramine over desipramine in SMD, this group has demonstrated the selective efficacy of clomipramine in a range of disorders that, although not necessarily strictly classified as SMD, are characterized by stereotypic symptoms. Thus in trichotillomania,44 nail-biting,45 and autism,46 clomipramine appeared more effective than desipramine, although results were not perhaps as robust as those seen in classical obsessive-compulsive disorder (OCD), which responds selectively and significantly to this SRI.47

Unfortunately, despite promising data in open trials of the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine in trichotillomania, subsequent controlled trials of these agents have been somewhat disappointing.48,49 There has been little work on the SSRIs in nail-biting. In autism, open and controlled trials indicate that the SSRIs may be useful in reducing symptoms such as self-injurious behavior,50 although again these effects are not perhaps as robust as clinicians would like.

Although dopaminergic agents have been a focus of attention in studies of the treatment of tics in Tourette's syndrome, there have also been a number of open-label reports and some controlled trials of serotoninergic antidepressants such as trazodone, clomipramine and the SSRIs.51,52 Open trials and clinical experience suggest that the SSRIs may be useful in reducing co-morbid OCD symptoms in Tourette's syndrome.53 Also, the addition of SSRIs to antipsychotic medication may be effective in the treatment of some patients with Tourette's.54

In summary, a series of studies has shown that clomipramine is superior to desipramine in reducing stereotypic behaviors in a range of psychiatric disorders. Unfortunately, the therapeutic effect of the SRIs in SMD, trichotillomania,
and autism is not always as robust as in OCD. Nevertheless, there is increasing evidence that this medication class is useful in some patients with these disorders. A combination of dopamine blockers and SRIs may also be useful in reducing various stereotypes.

Other Serotonergic Agents

Other agents with serotonergic effects have also been studied for the treatment of self-injurious stereotypes in patients with mental retardation. 5-Hydroxytryptophan (5-HT) has been shown useful in only a minority of open studies in mental retardation and Lesch-Nyhan syndrome. Similarly, tryptophan was ineffective in a controlled trial of nocturnal bruxism in intellectually normal patients. Buspirone (15-45mg/day), a 5-HT1A agonist, was somewhat effective in small groups of adults with mental retardation and self-injurious behavior. Trials with eltoprazine, a selective 5-HT1A and 5-HT2A agonist, has provided conflicting evidence for efficacy.

A double-blind trial of fenfluramine found that this agent was useful for weight loss and other-directed aggressive behavior in Prader-Willi Syndrome patients, but did not affect self-injurious behavior (SIB). Similarly, despite early reports of the efficacy of fenfluramine in open trials in autism, subsequent controlled trials have been somewhat disappointing.

A number of agents, such as lithium and B-blockers, have multiple neurotransmitter effects, including serotonergic effects. Although early studies in this area suffered from methodological flaws, lithium has long been used with some apparent success in the treatment of self-injurious behavior and aggressive behaviors in patients with mental retardation.

More recently, propranolol (90-410mg/day) was reported to reduce self-injurious behaviors and aggression in a small sample of patients with mental retardation. Furthermore, in a controlled study of similar subjects, pinadol (40mg/day) was significantly more effective than placebo in patients with mental retardation.

In summary, although SRIs have been best studied, a number of other medications with various serotonergic effects may also be useful in decreasing stereotypic symptoms, and deserve further controlled study.

OPIOID AGENTS

A number of authors have suggested that the opioid system plays a crucial role in mediating self-injurious behaviors. In animal work, opioid agonists may induce autoaggression, and opioid antagonists may be particularly effective in reducing self-injurious stereotypes in younger animals. Indeed, it has been suggested that excessive opioid activity underlies self-injurious behaviors. However, an alternative hypothesis emphasizes that pain associated with self-injurious behavior results in release of brain endorphins and draws a parallel between such endogenous release of endorphins and addiction to an exogenous substance. It has also been argued, however, that opioid effects on self-injury may be mediated primarily via the dopamine or serotonin system.

There is some evidence that the opiate antagonists naloxone and naltrexone lead to a reduction in frequency of self-injurious stereotypes in different patient populations, including those with mental retardation and autism. However, the total number of patients in such studies is relatively small and the study designs of this work have been criticised.

Indeed, in a recent placebo-controlled study of 32 subjects with mental retardation and self-injurious behavior and/or autism, naltrexone (50mg/day) failed to have an effect on self-injurious behavior and indeed increased the incidence of stereotypic behavior. Although this finding does not entirely rule out a role for the opioid system, it further emphasizes the need for caution in drawing conclusions from open trials of treatment for self-injurious behavior in this population.

Opioid agents have also been studied in conditions not classified as SMD but characterized by stereotypic symptoms. Thus, naltrexone was found useful in a placebo-controlled study of trichotillomania. Also, a number of studies have suggested abnormalities of the opioid system in Tourette's Syndrome, with both opioid agonists and antagonists having been reported to be useful in some cases. Indeed, McConville and colleagues suggest that Tourette's patients may show dynamic fluctuation in the functional status of opioid neurotransmission rather than simple hypoactivity or hyperactivity. Nevertheless, given the relative lack of data, opioid agents cannot yet be definitively recommended in this disorder.

OTHER AGENTS

The use of benzodiazepines for self-injurious stereotypes in mental retardation has not been well studied. Further attention should perhaps be paid to the role of the GABAergic system in self-injurious stereotypes in mental retardation. From a clinical viewpoint, however, the possible risks of disinhibition and of dependence should be borne in mind when considering the use of these agents.

The anticonvulsant valproic acid was effective in reducing self-injurious behavior and aggression in 12 of 18 patients with mental retardation and affective symptoms in a 2-year open trial. Positive response to valproate was associated with a past history of seizure disorder. Again, the possible use of anticonvulsants for self-injurious stereotypes in a subgroup of patients with mental retardation seems a useful avenue for further study.

Controlled trials of clonidine demonstrate efficacy in the treatment of Tourette's disorder, with reduction in tics, compulsive behavior, and
other target symptoms. It seems likely that noradrenergic, dopaminergic, and serotonergic systems have important interactions in Tourette's disorder.

CONCLUSION

The pharmacotherapy of SMD and of stereotypies remains in its infancy. Early work supported the use of typical antipsychotics, but there are important concerns about the efficacy and safety of these agents. More recently, there has been a focus on the SSRIs, which appear useful for some patients with stereotypic symptoms in a range of different disorders. Nevertheless, further controlled and long-term studies are needed to formulate rational approaches to the pharmacotherapy of SMD.

There is a large database of studies on the neurobiology of stereotypies in animal models, which may usefully be drawn on in planning future clinical studies. A growing series of medication trials in domestic animals with stereotypic behaviors may also prove relevant to human studies. Basic studies of the interactions between the dopamine and serotonin systems may be particularly important in view of the apparent usefulness of the newer antipsychotic agents (which have both dopaminergic and serotonergic effects) and of combinations of dopaminergic and serotonergic agents in treating stereotypies.

Despite this focus on serotonin and dopamine, it is possible that certain forms of stereotypies involve entirely different neurochemical systems (for example, the immune mechanisms that are currently hypothesized to play a role in some OCD patients). Certainly, a range of different agents and augmentation strategies appear useful in at least some patients with stereotypic symptoms. Future work will undoubtedly shed more light on the neurochemistry and neuroanatomy of SMD. We hope that ultimately pharmacologic treatments of this disorder will prove to be more rational and more effective.

REFERENCES

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