Aripiprazole–Olanzapine Combination for Treatment of Schizophrenia

Dear Editor:

Recent literature is equivocal about antipsychotic combination in schizophrenia (1). However, the advent of the new antipsychotic aripiprazole, which has a mechanism of action different from other atypical antipsychotics, rekindles interest in this field. I describe a patient with schizophrenia showing partial response to olanzapine alone, but showing a marked improvement in symptoms (particularly the negative symptoms) on augmentation with aripiprazole. The possible mechanism of aripiprazole’s efficacy in negative symptoms is discussed.

Case Report

Mrs A, a 47-year-old woman with a long-standing history of schizophrenia, was admitted with a psychotic exacerbation precipitated by discontinuation of medicines. On mental status examination, she had marked psychomotor retardation, poverty of speech, flat affect, persecutory and referential delusions, loosening of association, and poor insight and judgment. She scored 122 on the Positive and Negative Symptom Scale (PANSS) with a negative score 46, positive score 25. The patient was restarted on her previous antipsychotic; namely, olanzapine titrated to 20 mg daily, with further increase precluded by increased sedation. She was on potent D2 antagonists may benefit from an augmentation strategy (2). Aripiprazole also shows a dose-dependent D2 receptor occupancy above 85% at dosages of 10 to 30 mg daily (3). With both olanzapine and aripiprazole having a high D2 receptor occupancy, one may question the rationale of combining these drugs. However, even at D2 occupancy values above 90%, extrapyramidal symptoms (EPS) are not observed with aripiprazole (3). This may be attributed to aripiprazole’s being a partial agonist at the D2 autoreceptor. It would be interesting to explore how this mechanism may contribute toward improvement in negative symptoms.

Negative symptoms of schizophrenia have been hypothesized to result from a decrease in tonic dopamine transmission (4). Further, D2 autoreceptors tonically inhibit dopaminergic neurons (5). Stimulation of these receptors, as is the case with aripiprazole, induces their desensitization, leading to increased dopamine release (4). This novel mechanism may underlie aripiprazole’s low propensity to cause EPS and may also contribute toward its possible efficacy in negative symptoms. The previous generation of atypical antipsychotics, including clozapine, relies mainly on 5-HT2A antagonism for their greater efficacy in negative symptoms (6). Though aripiprazole also has a 5-HT2A antagonistic action, its role as a dopamine autoreceptor agonist may provide additional benefits for countering negative symptoms. Indeed, the study by Kane and colleagues showed that 15 mg daily, but not 30 mg daily, of aripiprazole produced a significantly greater improvement in PANSS negative subscale score, compared with placebo (7). There is some evidence to suggest that dopamine autoreceptor agonists do improve negative symptoms in schizophrenia patients with predominant negative symptoms (8). As aripiprazole acts as a dopamine agonist in the presence of significant receptor reserve for dopamine (which may be secondary to receptor upregulation following a hypodopaminergic state) (9), it can be speculated that schizophrenia patients with residual negative symptoms who are on potent D2 antagonists may benefit from the addition of small doses of aripiprazole. Further studies of aripiprazole at lower and higher dosages in primary negative symptoms are encouraged.

References

**Improvement of Torticollis With Quetiapine in a Schizophrenia Patient**

Dear Editor:

In patients with schizophrenia, extrapyramidal symptoms (EPS) and tardive syndromes are commonly associated with exposure to conventional antipsychotics such as haloperidol and can lead to noncompliance. Atypical antipsychotics are much less likely to cause such side effects and often reduce these problems (1), though there are differences among drugs within this class (2). Here I report the history of a patient with schizophrenia who suffered distressing, involuntary contractures of the neck muscles (torticollis).

**Case Report**

Miss C, aged 35 years, was diagnosed with paranoid schizophrenia at age 24 years, while attending university. She received intramuscular, short-acting haloperidol (1 dose of 10 mg) and developed torticollis. Torticollis persisted for 1 year, despite treatment with a reduced dosage of haloperidol, a dosage of chlorpromazine (maximum 400 mg daily) and several side effect medications (specifically, benzoprine, procyclidine, amantadine, and lorazepam). A neurological consultant believed the muscle contractures were secondary to the antipsychotic medication. Following the failure of tetrabenazine (maximum 75 mg daily) to reduce the contractures, the patient and her family refused antipsychotic medication, believing the cure was worse than the illness. Over the next 5 years, Miss C attended the emergency department 18 times, with agitated or aggressive behaviour and was treated with various antipsychotics, with moderate response and little improvement in neck dystonia. Outside of hospital, she refused medication and was largely housebound.

In May 1998, the family brought her to hospital because she had threatened her father with a knife. She was experiencing auditory hallucinations and believed an outside force was controlling her thoughts. She had a marked twisting of the neck, which she found very distressing. Her total score on the Positive and Negative Syndrome Scale (PANSS) was 108 and the neck dystonia was considered severe on the Clinical Global Impression of severity of dystonia scale (the Extrapyramidal Symptom Rating Scale).

A trial of clozapine was undertaken, but despite moderate improvement in neck dystonia, clozapine was discontinued after 4 weeks because of neutropenia. The patient then received an increasing dosage of quetiapine (50 to 800 mg daily over 3 weeks) and demonstrated a moderate initial response. Over 6 weeks, after a dosage of 800 mg daily was achieved, her delusions abated, her agitation ceased, and she stopped responding to auditory hallucinations. The dystonic neck posture normalized, with neck muscle spasms causing only occasional concern. Her PANSS total score was 67, and severity of dystonia was mild.

This case demonstrates that switching to second-generation antipsychotics may improve tardive dystonia. Both clozapine and quetiapine have demonstrated placebo-level EPS across the dosage range (3,4). However, clozapine is associated with agranulocytosis and requires regular blood monitoring (5), which may decrease its acceptability to patients. Further, quetiapine has demonstrated efficacy in patients who have switched from other antipsychotics following an inadequate response or intolerance (6,7). In the treatment of schizophrenia appropriate side effect management is important in ensuring that poor compliance, and subsequently poor outcome, are avoided. The patient and her family were very pleased with the resolution of the neck dystonia with quetiapine, and as a result, she continues on her medication, has returned to part-time education, and remains in good health.

**References**

2. Taras D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23–45.

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To investigate present and lifetime behavioural patterns in a group of adolescents \((n = 26, \text{mean age } 12.9 \text{ years, range 10 to 16 years})\) with CD we used Baum and Walker’s modified version of the Child Behaviour Checklist (CBCL), where parents are required to rate their children within 2 age periods: from birth to age 3 years (infancy) and from age 4 to age 10 years (childhood). The scores of the CD group were compared with those of a nonclinical group. From this study, CD seems to emerge during adolescence as a disturbance presenting a clear overlap between externalizing (score: 72) and internalizing (score: 68) dimensions. Such an overlap is still present during childhood when significant differences between childhood and adolescence do not emerge (internalizing score: 68 vs 68: \(P = 0.94\); externalizing score: 72 vs 70: \(P = 0.32\)). From birth to age 3 years, the comparison between CD and the control group shows significantly higher mean scores for the CD group on both internalizing (63 vs 42: \(P < 0.001\)) and externalizing (57 vs 38: \(P < 0.001\)) scales, but with mean scores falling in the clinical range only for the internalizing dimension.

These data permit us to hypothesize that CD has both internalizing and externalizing antecedents during childhood, although families consult at adolescence only for externalizing symptoms. Our findings also support the hypothesis that CD has relevant symptoms in infancy, thus allowing us to underline the importance of early internalizing antecedents in CD. According to Aronen (2), the internalizing symptoms in our sample precede later externalizing problems. Luby also found an unexpectedly high level of internalizing psychopathology in a group of externalizing children under 5 years of age (3). This high level of internalizing psychopathology found in externalizing children might account for high rates of comorbidity and for difficulties in differential diagnosis with preschool children having bipolar disorders. The question of comorbidity with mood and anxiety disorders is very complex for CD, representing an area for further investigation that may have important clinical implications for treatment of young children with externalizing disorders. Moreover, depressive symptoms in childhood should be addressed to prevent later psychiatric problems, especially aggression, poor adaptive functioning, and low self-esteem (2).

Finally, a heterotypic developmental continuity can be hypothesized (4), where internalizing problems first occur in infancy and externalizing problems emerge later during childhood and mature during adolescence, giving rise to a clinical pattern of mixed internalizing and externalizing disorder. This perspective seems to disconfirm the alternative hypothesis that internalizing symptoms emerge as a consequence of externalizing problems.

### References


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### Travel Time and the Use of Psychiatric Outpatient Clinic Services in Coastal Northern Norway

**Dear Editor:**

Studies from other countries have found that travel time is of importance to the utilization of psychiatric services, suggesting that most patients will not travel over 30 minutes for service (1). Northern Norway is sparsely inhabited, and inhabitants are accustomed to travelling. We examined whether travel time was of importance to service utilisation at the outpatient clinic at Stokmarknes, Nordland. The catchment area comprises 2368 km\(^2\) and had 31 629 inhabitants in 1997 (2). The population is ethnic Norwegian, with a minority population of Samis and African and Asian refugees. Types of employment include administration, education, health services, private business, fishing, farming, and the military; 46% of the population live in 5 towns, with the remainder living in sparsely populated areas. The clinic also gives occasional consultations (that is, less than 10%) in general practitioner (GP) offices outside of Stokmarknes.

We retrospectively compared the clinic’s record of patients treated from 1992 to 1996 with publicly available population figures (2). Travel time was calculated from zip codes and from information gathered from local bus and ferry companies. Geographical factors made 35 minutes a natural division point. Of the inhabitants, 10 996 (34.8%) had a travel time of 35 minutes or less (group 1). The remaining 20 633 inhabitants (65.2%) exceeded a travel time of 35 minutes (group 2). Of 1834 patients treated, 51.9% had a travel time of 35 minutes or less. A significantly higher proportion living within 35 minutes of the clinic had used the clinic’s services (8.6% vs 4.3%, \(\chi^2 = 250, P < 0.001\)). The mean travel time in group 1 was 22.1 minutes (range 0 to 35 minutes); in group 2, it was 99.5 minutes (range 50 to 130 minutes). The mean age in group 1 was lower than in group 2 (40.5 vs 43.5 years). The percentage of women in group 1 was nonsignificantly higher (59.4% vs 56.4%, \(\chi^2 = 1.70\)).

In Norway, the number and level of activities in smaller local clinics has increased, following the belief that smaller local facilities are preferable to, and more accessible than, larger central facilities. However, little effort has been made to study whether local facilities are in fact sufficiently accessible to people in the catchment area. Although north Norwegians are accustomed to travelling longer distances to obtain specialized medical services, we find that travel time remains

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important to the use of psychiatric outpatient services. Though we lack information, we believe that a combination of fewer referrals and more missed appointments explains why the rate of utilization is lower in group 2 than in group 1. Other possible explanations are differences in mental health, tendency of people with mental illness to drift toward the towns, and higher tolerability toward persons with mental illness among GPs and other people in the periphery.

References


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Respiratory Panic Disorder Treatment With Clonidine

Dear Editor:

Clonidine is known to block alpha-2 receptors in the locus coeruleus, and for theoretical reasons, it would seem a good antipanic drug. Few clinical trials have been conducted with clonidine for the treatment of panic disorder (PD) (1,2). In a small series, two-thirds of patients initially responded, but the therapeutic effect tended to be lost in some weeks, despite continuation of dosage (1). In this study, we report 2 cases of respiratory PD patients who were successfully treated with clonidine in the Laboratory of Panic and Respiration of Rio de Janeiro.

Case Report 1
Miss A is a white student, age 20 years. The patient began having panic attacks 3 years ago, with symptoms including sweating, shivering, tachycardia, dyspnea, and an intense fear lasting from 5 to 20 minutes. Two months before her first evaluation, the patient suffered new panic attacks with feelings of dyspnea, shortness of breath, tachycardia, fear of choking, and fear of dying. She described a fear of being home alone and of riding buses or other public transportation; she therefore avoided these situations. She underwent several laboratory examinations, all with normal results. She was initially treated with 0.15 mg daily of clonidine. After 6 weeks, she was taking 0.30 mg daily of clonidine and achieved full remission of the panic attacks and phobic avoidance. In the initial 2 weeks of treatment, the patient described feelings of mild dizziness and nausea.

Case Report 2
Miss C is a white college student, age 23 years. The patient described recurrent panic attacks during a 1-year period, with feelings of dizziness, tachycardia, trembling, heat spells, dyspnea, and a fear of becoming insane (lasting 10 to 15 minutes). The panic attacks occurred mainly in closed places, such as restaurants and bookstores. The patient discovered that by avoiding these situations she could decrease the frequency of the panic attacks, and she progressively interrupted all daily activities until she seldom left the house at all and developed an agoraphobic behaviour. Laboratory and clinical exams were normal. She was initially treated with 0.15 mg daily of clonidine, increased to 0.30 mg daily after 4 weeks of treatment, which fully remitted her panic attacks. At the sixth week of treatment, the patient continued her studies with the same dosage of 0.30 mg daily of clonidine. She described feelings of somnolence in the initial 2 weeks of treatment.

Both patients obtained panic-free status, reduced anxiety levels, and better functioning after clonidine administration for 6 weeks. An interesting finding is the remission of panic attacks with clonidine as early as the 4th week of treatment. Clonidine was well tolerated by the patients. All patients were classified as respiratory PD subtype, according to Briggs and colleagues’ criteria (3). This subtype may have a favourable clinical response to clonidine. Because of its specific adrenergic action, clonidine may be an effective tool for investigating and elucidating abnormalities in a noradrenergic system in patients with PD, and it may play a role in relieving symptoms of anxiety caused by noradrenergic hyperactivity.

References


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