Letters to the Editor

Modafinil Treatment of Excessive Sedation Associated With Divalproex Sodium

Dear Editor:

Divalproex is recognized as a first-line agent in the treatment of bipolar disorders (BDs) (1). However, sedation can be an unwelcome side effect of divalproex sodium treatment (2), and unwanted side effects can lead to patient noncompliance (3). Ultimately, noncompliance can contribute to hospitalizations (4). I present 2 cases in which patients treated with divalproex sodium for BD experienced excessive sedation that responded favourably to modafinil.

Case Report 1
Mr A is a 35 year-old man suffering from BD I diagnosed according to DSM-IV criteria (5), as well as from methamphetamine abuse. His most recent episode was depressed, and he presented in remission. He was taking bupropion sustained release (SR) 150 mg twice daily and divalproex 750 mg twice daily. Mr A complained that, since restarting divalproex 1 month prior to consultation, he was sleeping 12 to 14 hours daily and unable to work. Laboratory examination showed a divalproex level of 85 µg/mL. His complete blood count, hepatic enzymes, serum electrolytes, lipase, amylase, and ammonia were all within normal limits, and a urine drug screen was negative for illicit substances. Mr A denied the use of alcohol and was enrolled in an outpatient rehabilitative program; however, he was not as active as he wanted to be, owing to excessive sedation. To diminish the excessive sedation, he agreed to a reduced divalproex dosage, and this medication was decreased from 750 mg twice daily to 500 mg twice daily. A serum divalproex level was maintained in the therapeutic range at 67 µg/mL. Unfortunately, he continued to experience daytime somnolence. He agreed to a trial of modafinil initiated at 100 mg daily. He did not experience any side effects and noted decreased sedation within 1 week of starting modafinil. After 1 week of modafinil at 100 mg, his dosage was increased to 200 mg daily, with marked improvement. He was sleeping 8 hours nightly and felt awake during the day. He was able to participate in family life and was able to find employment after having been unemployed for 9 months and at one time thinking of filing for permanent disability. His divalproex levels have remained within the therapeutic range while he is on modafinil. He remains stable at 1 year, with no trigger of hypomanic or manic symptoms associated with modafinil.

Case Report 2
Mr B is a 27-year-old man diagnosed with BD I and obsessive–compulsive disorder (OCD) according to DSM-IV criteria (5). His most recent episode was manic. He was taking divalproex 500 mg every morning and 750 mg at bedtime, sertraline 200 mg daily, quetiapine fumarate 75 mg at bedtime, and clonazepam 1 mg daily. He had recently been hospitalized but had been compliant for 2 months on the medications. He complained of sleeping 14 hours daily. His serum level of divalproex was 87 µg/mL. The rest of his laboratory examination included a complete blood count, hepatic panel, pancreatic enzymes, ammonia, serum electrolytes, and urine drug screen, all of which were unremarkable. The clonazepam and quetiapine were tapered off to determine to what extent they might have contributed to Mr B’s sedation. After discontinuing the clonazepam and quetiapine, he slept about 12 hours nightly. The divalproex was decreased by 250 mg at night with no decrease in next-day sedation. Mr B agreed to a trial of modafinil started at 200 mg daily. He experienced a mild anxious feeling. Within 1 week, his daytime sedation was markedly improved, and he was averaging 7 to 8 hours of sleep nightly. He remains stable at 1 year with no noted exacerbation of mood symptoms or worsening of his OCD. As well, while on modafinil, his subsequent divalproex serum levels have been therapeutic.

Modafinil is approved by the US Food and Drug Administration to treat excessive daytime somnolence associated with narcolepsy. It is chemically unrelated to the psychostimulants (6). It is thought to alter the balance of GABA and glutamate, resulting in activation of the hypothalamus (7,8). Modafinil has been used as an adjunct in the treatment of major depression, allowing patients to achieve remission as well as targeting residual tiredness (9). Makela and others recently reported the successful use of modafinil to treat sedation induced by antipsychotics in 3 patients (10). Although I reduced my patients’ medication and tapered concomitant medications that could have contributed to sedation, I felt that modafinil could alleviate their excessive sedation. Because it is structurally unrelated to traditional stimulants, I did not expect to trigger hypomania or mania. In Mr A’s case, I considered the possibility of substance abuse, although modafinil does not appear to have abuse potential (11). Modafinil also did not appear to alter serum levels of divalproex, which is another important consideration.

To my knowledge, this is the first report of using modafinil to treat excessive sedation associated with divalproex sodium. Case reports must be interpreted with caution; however, modafinil may be useful in treating excessive sedation associated with divalproex sodium. Further studies in a controlled manner are encouraged.

References
Dear Editor:

Hallucinations and delusions are frequent side effects of dopaminergic treatment in Parkinson’s disease (PD) patients. These patients do not generally tolerate typical antipsychotic therapy with D2 antagonist drugs. Ziprasidone is a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. Clinical trials suggest that the drug is effective in treating schizophrenia (1). We report remission of psychosis and improvement of motor symptoms in a PD patient taking ziprasidone.

Case Report

Mr A, a 70-year-old man with a 16-year history of PD, was admitted to our department for levodopa-induced psychosis. Antipsychotic treatment with clozapine had been effective but had to be discontinued owing to agranulocytosis. At admission, the patient was treated with L-DOPA/carbidopa 1200 mg, L-DOPA/benserazide 375 mg, entacapone 1200 mg, and quetiapine 800 mg daily. He had pronounced visual, auditory, and tactile hallucinations, as well as delusions of persecution. Physical examination showed hypomimia, stooped posture, and a slight resting tremor of the right hand. There were infrequent (< 1 daily) off-episodes, with akinesia and rigidity lasting up to 1.5 hours. Otherwise, activities of daily life were only moderately affected. The Uniform Parkinson Disease Rating Scale (UPDRS) score was 43/199. The results of laboratory tests and the findings on cranial magnetic resonance imaging, ECG, and EEG were unremarkable.

Ziprasidone was initiated at 40 mg once daily and increased to 80 mg once daily over 3 days. Within 2 weeks, delusions and hallucinations subsided, and motor function improved fundamentally. Sitting, walking, dressing, showering, and eating without assistance became possible. On discharge, the UPDRS score was 42.

Ziprasidone is one of the newer atypical antipsychotic drugs; these drugs tend to cause fewer extrapyramidal side effects (EPSEs) than classic neuroleptics. Within the group, atypical neuroleptics have varying propensities to cause EPSEs. Clozapine appears to be superior in this regard and is widely recognized as a standard treatment for dopaminergic psychosis in PD. Experience with ziprasidone is lacking, and EPSE frequency has been estimated to equate that of olanzapine, which is not well tolerated in PD (2). In our opinion, however, the choice of a neuroleptic drug in PD should depend on the probability of drug-induced Parkinson’s symptoms and not of drug-induced dystonia, hypokinesia, akathisia, and myoclonus—all of which are EPSEs. Two substances with the same overall EPSE frequency may not be equally safe in patients with PD. Akathisia has been reported with ziprasidone (3), and we have also encountered acute dystonia. However, Parkinson’s symptoms occur rarely if at all, and therefore, ziprasidone may become a real alternative treatment for PD psychosis.

References

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Combined Oral Venlafaxine and Intravenous Clomipramine-A: Successful Temporary Response in a Patient With Extremely Refractory Depression

Dear Editor:

We report a case of a married woman, aged 33 years, with treatment-refractory dependent and borderline personality disorder and major depression with atypical features, diagnosed according to DSM-IV criteria. She began to experience free-floating anxiety and incomplete panic attacks at age 26 years, which were soon followed by major depression. Two years later, at age 28 years, she had already attempted suicide once by swallowing pills a couple of months prior to presenting. Her psychiatric family history was blank.

Given 1 mg dexamethasone, she was a nonsuppressor on the dexamethasone suppression test (DST) (based on the cut-off point of 5 µg/dL plasma cortisol) and had blunted response to 30 mg dexfenfluramine challenge test (cut-off 50 µU/L prolactin). Brain-imaging single photon emission computed tomography (SPECT) showed increased regional cerebral blood flow in the frontal lobes (+1.5 sd) and reduced regional cerebral
blood flow (−0.3 to −1.4 sd) in the rest of brain areas.

The patient received the following adequate but unsuccessful treatment trials (including combinations) lasting at least 4 months each: 60 mg fluoxetine, 375 mg venlafaxine, 40 mg haloperidol, 6 mg risperidone, lithium (plasma levels 1.0 mEq/L), carbamazepine (plasma levels 9 µg/mL). She also had 8 clomipramine infusions (maximum 4 ampoules), with partial and unstable response for a couple of days. She refused ECT. During the last year, she has had rare mood-congruent auditory hallucinations.

We decided to try a more aggressive treatment with high dosages of intravenous (IV) clomipramine plus oral venlafaxine. The maximum dosage reached at day 15 was 6 ampoules IV clomipramine plus 225 mg oral venlafaxine.

On day 15, the patient responded with a dramatic remission of symptoms, almost to normothymic state. Her overall Hamilton Depression Rating Scale (HDRS) score decreased from 37 to 11, and her Hamilton Anxiety Rating Scale score decreased from 46 to 11. On the following HDRS indexes, her scores were as follows: depression symptoms decreased from 18 to 2; anxiety symptoms decreased from 8 to 6; insomnia symptoms decreased from 6 to 3; and nonspecific symptoms decreased from 5 to 0. This remission lasted for 37 days; then, obeying auditory hallucinations, the patient unsuccessfully attempted suicide by swallowing 30 tablets of diazepam 10 mg and thioridazine 30 mg. The mood change was acute, occurring within a few hours.

Clomipramine is not approved by the FDA for the treatment of depression; in continental Europe, however, it is considered the most effective agent, although there are only 5 published studies on its use to treat refractory depression (1–5). Our report is the first one on the combined use of oral venlafaxine and clomipramine infusions. The only prior combined treatment reported concerns maprotiline.

The usual practice of infusions suggests starting with one-half ampoule of clomipramine and adding 1 ampoule every day to reach a maximum of 5 to 6 ampoules. Anecdotal data report higher dosages of 8 to 9 ampoules daily.

References

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Doxepin Increases Serum Cholesterol Levels

Dear Editor:

Doxepin is a well-known nonselective tricyclic antidepressant (TCA) that has been marketed in Germany for over 30 years and is still frequently applied. It causes common and group-specific side effects, including metabolic changes such as increases and decreases in blood sugar levels (1). Other metabolic changes in patients treated with TCAs have occasionally been reported. For example, increased serum cholesterol in 24 patients treated with imipramine for panic disorder was observed (2). Conversely, the same investigators also reported decreased high-density lipoprotein (HDL) cholesterol in patients on imipramine for panic disorder. Both depression patients and patients suffering from panic disorder showed an increase in the ratio of serum total cholesterol to HDL cholesterol under imipramine medication (3). After an average of 7 months of nortriptyline treatment, 26 depression patients showed significantly elevated levels of triglycerides and very-low-density lipoproteins (VLDL); however, they did not show significant changes in cholesterol levels (4). Further, it has been shown that the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine increases serum cholesterol to over 20% above the upper limit of normal in approximately 15% of patients (1).

We describe a patient who showed a significant isolated elevation of serum cholesterol while on monotherapy with doxepin.

Case Report

A 32-year-old white woman suffering from severe recurrent depression without psychotic symptoms, diagnosed according to ICD-10 criteria, had been on venlafaxine for 20 weeks, with serum cholesterol levels within the normal range (is 201 to 221 mg/dL). She switched from venlafaxine to doxepin, and by week 21, her cholesterol rose to 271 mg/dL. In week 25, her cholesterol reached a maximum level around 320 mg/dL, which persisted for 20 more days. After she stopped taking doxepin and switched to reboxetine in week 27, her serum cholesterol gradually fell within 3 weeks from 312 mg/dL to 209 mg/dL. During this time, reboxetine was given as an antidepressant. Throughout the entire period, triglyceride levels were within the normal range.

Discussion

At present, there are limited and contradictory data with respect to changes in cholesterol levels in patients on antidepressant medications. Apart from limited data on TCAs, there are also reports on the effects of other antidepressants on lipid metabolism. A prospective study described a cholesterol-lowering effect...
of fluvoxamine (5). In a controlled study comparing fluoxetine and trazodone, the trazodone group, but not the fluoxetine group, exhibited significantly decreased cholesterol after 6 weeks of treatment (6). Elevated cholesterol levels during treatment with antidepressant medications appears to be noteworthy from 2 perspectives.

First, it is presumed that degeneration of minor cerebral vessels, possibly owing to impaired lipid metabolism, leads to a disruption of the frontosubcortical circuits that regulate mood, cognition, and movement (7). If TCAs elevate cholesterol levels, they may increase the risk of vascular depression, which would also be an unwanted side effect of this medication.

Second, since the early 1990s, a correlation between serum cholesterol levels and suicidal ideation or depression has been the subject of debate. To date, the reported results are contradictory; they range from increased suicide risk in persons with low serum cholesterol levels (8,9) to improved mood with dietary lowering of serum cholesterol (10) and include a nonnegative effect on mood symptoms (11). It is possible that low serum levels or lowering of the serum cholesterol correlate differently to mood symptoms in emotionally healthy persons and in depression patients, that a decrease in cholesterol owing to diet or owing to treatment with cholesterol-lowering medications produces different effects, and that this affects the sexes differently. To our knowledge, this is the first report observing increased serum cholesterol levels in a patient treated with doxepin.

Besides the need to examine the correlation of mood symptoms and the serum levels of various lipid fractions, additional studies, including prospective studies, of the changes in serum cholesterol and triglyceride levels during therapy with TCAs and other antidepressants are necessary. We recommend screening patients treated with TCAs for changes of serum cholesterol levels, especially patients at risk for cardiovascular diseases.

References


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Re: Suicide: The Persisting Challenge

The recent editorial by Dr Isaac Sakinofsky (1) and the other articles appearing in the June 2003 issue of the Journal discuss a most important aspect of psychiatric practice. People at risk for suicide are vulnerable to various situations, some of which have been identified and accepted. For example, the replacement of coal gas, with its heavy concentration of carbon monoxide, by natural gas resulted in a marked drop in suicides. The use of electroconvulsive therapy (ECT) also contributed positively to preventing suicides. Unfortunately, all innovations—such as the replacement of imipramine by the monoamine oxidase inhibitors and later the selective serotonin reuptake inhibitors—have been followed by an upsurge of suicides. I recall that, when I cautiously introduced imipramine, I was impressed by the markedly reduced number of patients requiring ECT. We had a fairly large Department of Psychological Medicine in the Teaching Hospital in Birmingham, UK, and because of a bed shortage, we developed comprehensive outpatient services and a day hospital as early as 1950. In the first year of using imipramine, we reduced the numbers requiring ECT by 50%, and in the following year, by another 50%. Thus, within 2 years, only 25% of all patients with severe depression had to have a full course of ECT. As the years passed, the number grew smaller, with the advent of lithium, we lowered them further.

We did not send these “suicides” to the several mental hospitals in the West Midlands of England. In fact, patients with severe depression were soon much less likely to be admitted to the mental hospitals in the region (2). In my 25 years in the unit, not one of my patients committed suicide, and I have since maintained this “score.” Management is a major factor in the treatment of patients with severe depression. If the family is involved, the risk explained, and their active cooperation secured, we should be able to get the patient over the major hurdle in a week or so. Preventing suicide is a major responsibility that psychiatrists have to face. It is about the only way to lose a patient. As already noted, it requires much attention to management; in this regard, psychiatrists have to resist the interference of the team, because a team can greatly disturb the management of actively suicidal patients. I used to say that 10 people who do not know are no better than 1 person who does not know.

I abolished the practice of issuing suicide caution cards to the nursing staff. I entered the following statement in the case notes: “In my opinion, this patient can be treated in the general ward of a general hospital.” The nursing staff were most grateful, for they were no longer overwhelmed with suicide caution cards that could not guarantee more supervision. In fact, this practice led to less...
supervision. It meant that the psychiatrist constantly reviewed the situation and immediately introduced appropriate treatment. The patient and relatives were grateful for speedy recoveries. After she had seen me writing this opinion on the chart, I recall the ward sister saying, “But Dr Sim, you are accepting the full responsibility.” I replied that that was why they paid me more. It is much easier to follow this course, for no time was wasted in debating policy with the team, whose only advantage is to ensure that nobody is to blame.

In Canada, young men with ready access to firearms are another source of suicide victims. The numbers are staggering, and I used them to illustrate a point when I was asked to present a paper at the 10th International Congress for Suicide Prevention and Crime Intervention (3). In 1 year, there were 150 homicides, while 1500 men under age 31 years committed suicide with firearms. They were mainly young men working on farms who had access to firearms while suffering from severe depression that was not recognized. I also suggested that the Canadian Rifle Association should be actively engaged in preventing this horrible loss and that affected young men be persuaded to hand over their weapons until they have been successfully treated. Again, a major aspect in this treatment is the capacity to manage the situation, and I am concerned that this aspect of psychiatric treatment receives little emphasis in psychiatrist training. There would be convulsions in parliament if 1500 troops were wiped out owing to poor management, but this horrible loss from suicide, which is preventable, is allowed to continue. Cosy indolence is a poor substitute for preventative measures.

Finally, drug houses should not be allowed to replace a drug that effectively treats severe depression with “pep pills” that have the capacity to release aggressive tendencies. There is much more to say—but not in a letter to the editor.

References

Dear Editor:

I was pleased that our recent In Review articles on suicide in young people (1–3) caught the interest of Dr Myre Sim, whose textbook on psychiatry I recall reading with enjoyment years ago. I found his reminiscences on a half-century of psychiatry practised in Birmingham and Ottawa most interesting, but as always, some of his opinions are controversial and require an answer. Healthy controversy can spur scientific research, and I am glad to see that none of Dr Sim’s fires have been dimmed. Unlike Dr Sim, however, some of your readers—like myself—will be unable to attribute causal effect to “upsurges in suicide” that may have occurred following the introduction of monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRIs). Indeed, the reverse is postulated in Scandinavia and some other countries, as stated in my editorial (1); the issue currently debated is whether this is indeed so or whether the decline is the result of other influences (4).

Dr Sim refers to the release of aggressive tendencies by the SSRIs; however, there is only anecdotal and putative evidence of this in a very small number of patients. In most depression patients, the SSRIs appear to modulate aggressive impulses, as one would anticipate on theoretical grounds. With regard to replacement of tricyclic antidepressants by “pep pills,” the literature does not show superiority of tricyclic antidepressants over SSRIs in large samples of depression patients (5,6), although there may be subtypes of depression that respond differentially.

Concerning Dr Sim’s references to the therapeutic team, I would not myself agree with statements such as “psychiatrists have to resist the interference of the team.” However, I agree strongly with his implicit message that communication among members of the team caring for suicidal people should be effective, the team should be highly trained, and a clear, detailed care plan should be put into operation by all team members. The psychiatrist carries the medical responsibility and should play a major role in determining the care plan and in training the team in the care of suicidal patients. It should not be forgotten, however, that nurses also carry nursing responsibility, as do the other disciplines.

Dr Sim has made a long and important contribution to psychiatry, and I hope he will continue to do so. He showed admirable courage in shouldering full clinical responsibility for suicidal patients on his wards and protecting his nurses. I was glad to be reminded of his presentation on gun control in Canada at the 1979 IASP meeting in Ottawa (7), which I also attended. Groundwork like his laid the foundations for successive waves of gun control legislation in Canada that, however controversial, carry the possibility of some suicide prevention, particularly among men.

References
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Depression and Alcoholism

Dear Editor:

Depression and alcoholism are associated with considerable morbidity, disability, and mortality and cooccur more commonly than expected by chance (1–3). The results of several large epidemiologic studies have demonstrated the extent of comorbidity between depression and alcoholism (4–7). The National Comorbidity Study found an odds ratio of 2.0 between major depression and alcohol dependence (95% CI, 1.6 to 2.6) (4). Similarly, the National Longitudinal Alcohol Epidemiology Study demonstrated that 32.5% of individuals with major depression met criteria for a lifetime diagnosis of alcohol dependence, compared with only 11.2% of those who did not meet criteria for major depression (5).

A recent study compared clinical parameters in 2 groups of depression patients according to the presence or absence of a lifetime diagnosis of alcohol dependence (8). The authors found that depression patients with a lifetime diagnosis of alcohol dependence had lower Global Assessment of Functioning Scores; were more likely to have borderline, schizotypal, and paranoid personality disorders and cannabis dependence; and reported more paranoia and interpersonal sensitivity, compared with depression subjects without a history of alcohol dependence. Another recent study compared clinical parameters and cerebrospinal fluid (CSF) monoamine metabolites in depression patients with and without a history of alcoholism (9). Subjects with depression and a history of alcoholism had lower CSF homovanillic acid levels, were more likely to be tobacco smokers, and had higher lifetime aggression and current suicide ideation scale scores than did subjects suffering from depression but without a history of alcoholism. The results of these 2 studies demonstrate that individuals with depression and a history of alcoholism are more impaired than subjects with depression but no history of alcoholism. Treatments may be less effective for depression patients with a history of alcoholism than for other depression patients (3,10). In addition, individuals with a history of alcoholism may be at risk for a relapse of alcohol misuse (10). Therefore, it is important to recognize a history of alcoholism in patients with depression.

A history of alcoholism may be overlooked in primary care and psychiatric clinics. The clinician may not be able to gather the appropriate history because of the patient’s uncooperativeness. Alternatively, the clinician may fail to conduct an appropriate diagnostic interview: clinicians sometimes do not ask the most basic questions about alcohol or substance use. All depression patients should be asked about their current and past alcohol and substance use and advised to abstain from alcohol and substance use. It is important to maximize the chance of long-term sobriety in patients with depression.

References


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Gains in Speeded Information Processing Following Clozapine Treatment of Schizophrenia

Dear Editor:

Recent studies have focused on the impact of novel antipsychotics upon schizophrenia’s core cognitive deficits. Clozapine is one of the agents within this domain, and evidence is growing to support its positive impact upon cognitive functioning, including processing speed (1–5). Because cognitive functioning has predicted functional outcome (6,7), use of agents that may improve it is likely to become increasingly important. Further, clozapine should not be considered a treatment of last resort, as is often the case in Canada. We describe clozapine treatment of a male schizophrenia patient and the marked increase in cognitive as well as vocational functioning subsequently observed.

Case Report

A 35-year-old single man who was a full-time graduate student and living independently was admitted to the Prevention and Early Intervention Program for Psychoses (PEPP) with a first episode of paranoid schizophrenia. Over the first 2 years of treatment, he continued to suffer from florid psychosis, was non-compliant with medication, and was hospitalized on 2 occasions. Trials of oral risperidone and olanzapine and depot intramuscular risperidone were undertaken, with only temporary and partial sobriety in patients with depression.

References

symptom relief. The patient remained enrolled in his PhD program but kept putting off his dissertation. Twenty-seven months into PEPP, he began a trial of clozapine.

At baseline cognitive assessment following entry into PEPP, the patient scored at or above average on measures of intellectual functioning, working memory, immediate and delayed auditory memory, delayed visual memory, and mental flexibility. Weakness (that is, a score 1 or more standard deviations below average) was demonstrated in immediate visual memory, concept formation, attention, and processing speed. The patient was not willing or able to tolerate the demands of testing again until 41 months after entering the program. At that time, he had been taking clozapine 400 mg daily for approximately 14 months. He showed significant improvement in positive and negative symptoms of psychosis. Significant gains in concept formation and attention were seen. Most notably, the patient demonstrated an improvement in speeded information processing, rising from over 2 standard deviations below average to 0.5 standard deviations below average (a gain of 31 points). Although he did not complete his PhD, he is now employed full-time in his field of study.

**Discussion**

The gain in processing speed following clozapine treatment was far beyond that reported in other studies (1–5), significantly greater than gains in other areas (suggesting differential impact), and not explained by practice effects. There were no changes in other cognitive domains. Since persistent clinical improvement and medication adherence was noted only after he started taking clozapine, the likelihood of cognitive gains predating clozapine is minimal.

Cognitive data from our centre involving a large sample of first-episode psychosis patients treated with novel antipsychotics (primarily risperidone) do not demonstrate the same degree of improvement in processing speed. This domain, in fact, remains an area of relative weakness, despite gains in other areas (8). Symptom reduction is also not likely to explain this gain. Reports on the relation between cognition and symptoms have been inconsistent in the literature and are often weak, at best (9–11).

Our results confirm that clozapine treatment effectively enhances neurocognitive function and suggest that significant gains are possible, particularly in the area of processing speed. This effect was demonstrated after an extended period of unsuccessfully treated illness; the reported case supports this medication’s benefit in stabilizing not only psychotic symptoms but also cognitive difficulties—even more than 3 years after the emergence of what appeared to be a treatment-resistant psychosis. This case demonstrates the need to consider introducing clozapine early, as well as the benefits of not waiting until several trials of other antipsychotics have been undertaken.

**References**


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**Problems With Crystallizing Phenomenology and Nosology in Adolescent Psychiatry**

Dear Editor:

Debate over the DSM-IV criteria for child and adolescent disorders continues, focusing on developmental modifications to symptom clusters such as bipolar disorder and posttraumatic stress disorder (PTSD) and their expression in children and adolescents (1,2). Findings from a recent study on PTSD showed that absence of the triad does not indicate a lack of posttraumatic stress problems; rather, such absence may be owing to developmental differences in symptom expression. As such, current diagnostic criteria may not be appropriate for children (2). Similarly, a study of major depression and dysthymia included pathological behaviour such as disobedience, which was found to be quite frequent in adolescents with dysthymia (3). Even though child or adolescent symptomatology may not fit the criteria for a diagnosis, there can be significant impairment, which is important for nosology and prognosis (4). We report on 3 cases wherein symptom description and expression were ambiguous as a function of verbal expression, intelligence, and age-related psychosocial stresses.
Case Report 1: Depression—Growing Pain or True Morbidity?
A 16-year-old boy was admitted for acute suicidal risk after his third appointment with a psychiatrist. He first presented with symptoms of depression and met the criteria for major depressive disorder (MDD). He was given a selective serotonin reuptake inhibitor (SSRI) and weekly appointments. After a night on the ward, the patient showed dramatic improvement in mood, sleep, appetite, and energy. Medication was discontinued and he remained euthymic. He had significant learned helplessness attributable to an underlying learning disorder. Further inquiry revealed an amorous crisis as the main precipitator. The patient was discharged with a diagnosis of situational reaction.

Case Report 2: Psychosis or Hypomania?
A 17-year-old boy of limited intellectual and cognitive functioning was escorted by police and admitted involuntarily for insomnia and acute onset of nonstop activity lasting 72 hours. His maternal family history was positive for schizoaffective disorder. He was very suspicious on the ward, refusing ward food and isolating himself from others. He had no insight regarding his mental state and was noncompliant with medication. A drug screen was negative, and he had no neurological abnormalities. He was granted appeal against his admission and left 4 days later with a discharge diagnosis of queried bipolar affective disorder. He was readmitted 7 days later for psychiatric assessment and observation over 14 days. He had periods of immobility, agitation, and extreme negativism that were consistent with catatonia. He also had frank paranoid delusions and ideas of reference. Administration of zuclopenthixol acetate (50 mg) led to amelioration of symptoms, but not to their previous discharge level. The patient’s discharge diagnosis was changed to schizophrenia, catatonic type. He was readmitted again 2 weeks later with a similar presentation. This time, he was transferred to a long-stay ward and put on depot neuroleptic owing to ongoing noncompliance.

Case Report 3: PTSD or Schizophrenia?
A 16-year-old girl with a history of sexual and physical abuse presented with periods of bizarre behaviour, auditory hallucinations, and persecutory delusions. At age 14 years, she had been diagnosed with PTSD attributable to chronic abuse; she did not respond to SSRI treatment. Previously, at age 12 years, she had been diagnosed with Asperger’s disorder. Observation and assessment over a 3-week period showed bizarre delusions with incongruent affect, third-person hallucinations, thought disorder, and severely impaired functioning. Neuroleptic medication provided mild symptom relief, but her psychotic symptoms remained for 8 months. Her diagnosis was changed to schizophrenia, disorganized type.

These cases demonstrate that a disorder tends to evolve over time as the brain develops, before crystallizing into an operational diagnostic entity. Patients who are behaviourally and emotionally immature may not fully meet existing diagnostic criteria, because these often fail to take developmental stage into account (5). In Case Report 1, the patient met criteria for MDD at his first consultation. However an adolescent’s first breakup can have a highly significant impact on symptom presentation. Further, the time period required by the DSM-IV may be inadequate for an adolescent. In Case Report 2, the patient’s extreme hyperactivity, disrespectful demeanour, and refusal to comply led to his behaviour being described as hypomanic, despite the absence of elevated mood and affect. Structured observation and assessment over time uncovered the underlying psychopathology and phenomenology. Note that catatonic symptoms are uncommon among adolescents. In Case Report 3, the patient’s diagnosis of Asperger’s disorder may have been a description of premorbidity to her later schizophrenic illness. The confusion arose from her known history of abuse; her presenting symptoms were attributed to dissociative phenomena rather than to positive symptoms of psychosis. The full presentation of schizophrenia can require the passage of 2 years to crystallize.

Note
These cases were previously presented as a poster at the World Psychiatric Association Symposium; June 2003; Vienna.

References

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Serotonin Syndrome With Prolonged Dysphagia

Dear Editor:
Serotonin syndrome (SS) involves central nervous system (CNS) serotonergic pharmacotoxicity. Sternbach’s proposed diagnostic criteria for SS require the association of a CNS serotonergic agent with at least 3 of the following: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, poor coordination, and fever (1). Radomski and colleagues have
confirmed the validity of Sternbach’s criteria (2). Mills reviewed 127 SS cases and reported neuromuscular features including myoclonus (57%), hyperreflexia (50%), tremor (49%), restlessness (42%), and ataxia (38%) (3). Prolonged dysphagia was not prominent in any of these cases (K Mills, personal communication, March 13, 2003). Dysphagia is not included in SS diagnostic criteria, nor is it commonly cited in case descriptions. Conversely, dysphagia is commonly seen in neuroleptic malignant syndrome (NMS), a potentially fatal psychotropic toxidrome involving dopaminergic hyperactivity. Dysphagia in SS may lead to its confusion with NMS, an important distinction recently reviewed by Birmes and colleagues (4). We report a case of SS associated with prolonged dysphagia, and we discuss a potential mechanism.

Case Report

Our patient was a 74-year-old white woman with a history of major depressive disorder. Her medical history included ulcerative colitis at age 25 years and aortic valve replacement at age 72 years. She presented with an acute onset of agitation, tremor, hyperreflexia, myoclonus, ataxia, mutism, and swallowing difficulties evolving 48 hours after trazodone was increased from 50 to 100 mg daily. Her other medications were citalopram 40 mg and clonazepam 4 mg, each taken daily during the previous 6 months for treatment of a major depressive recurrence. Comprehensive laboratory investigations were noncontributory. Cranial CT scan revealed diffuse age-related cortical atrophy but no acute vascular changes, confirmed by follow-up CT scan after 48 hours. In consultation with neurology and internal medicine, we diagnosed SS, stopped the medications, and instituted supportive treatment. We started lorazepam to prevent benzodiazepine withdrawal symptoms. A feeding trial resulted in severe coughing with poorly coordinated orolinguinal movements that impaired swallowing and speech. We continued intravenous hydration and nasogastric feeding. Six days after admission, the neurological symptoms were resolving, except for dysphagia. A bedside swallowing assessment revealed lingual tremor, poor tongue extrusion, mild reflex trigger delay, and mouth breathing during swallow. Coughing and distress during a feeding trial of thick liquids resulted in a regression of diet to gels only. Marked dysphagia persisted 25 days after admission, despite the resolution of all other neurological symptoms. A modified barium swallow revealed normal anatomy, with poorly coordinated tongue action and pharyngeal leakage coating the underside of the epiglottis without frank aspiration. The patient was eventually able to protect her own airway and tolerated gradual dietary advancement.

SS involves excessive stimulation of postsynaptic brainstem and spinal cord 5-HT1A receptors (1). In this patient, we observed SS with the combination of trazodone, citalopram, and clonazepam, all of which have serotonergic properties and no major mutual pharmacokinetic interactions (5). The brainstem swallowing centre is localized at the nucleus tractus solitarius (NTS) (6). In animal studies, microinjections of serotonin into the NTS inhibit the swallowing reflex (7). In patients with SS, serotonergic hyperactivity at the NTS may thus inhibit the swallowing reflex. We hope to inform clinicians of the potential for dysphagia in SS and we encourage monitoring for complications such as aspiration pneumonia during the recovery phase.

References