Dear Sir:

Drs Goldbloom and Garfinkel deserve to be complimented on their thoughtful and thought-provoking article (1). They have provided us with an important challenge in terms of our further thinking about psychiatric education in Canada. It is necessary that training programs begin to grapple with the issues that these authors have identified.

Although no paper on their topic could possibly be comprehensive in its nature, I would have hoped that they would turn their considerable analytic skills to grappling with 2 other major issues that will substantially impact on the training of psychiatrists in the future. These issues are 1) mental health—mental illness and 2) the dilemma of promotion and prevention in mental health.

Currently, some people argue that the inclusion of mental illnesses under the concept of “mental health” has possibly outlived its utility. Certainly in the popular mind (and potentially in the minds of many legislators), there is a simplistic and unrealistic perspective that considers an investment in “mental health” as an alternative to the provision of treatments for “mental illness.” Indeed, in some circles it has become fashionable to focus on “enhancing” the normative “mental health” of populations to the detriment of those individuals with serious mental illnesses.

The allocation of resources (particularly when these are limited) to the more “healthy” members of our communities at the expense of those with illness is unfair and morally indefensible. Regrettably, this type of perspective is only too prevalent in the history of psychiatry. In past eras, much of this differential allocation of scarce resources has been at the level of the individual practitioner of psychiatry. The difficulty that we as a society seem to be facing now is that this reallocation may become institutionalized. The danger of this is that individuals suffering from mild difficulties (or no difficulties at all) may be preferentially treated to resources that will be taken from those with a severe and significant mental disorder.

One of the major issues that training programs need to address, both within their own walls and the wider community, is the importance of providing effective and cost-efficient treatment for individuals with serious mental illnesses. Psychiatry of the future cannot abrogate its responsibility to those who suffer from serious mental illness. Certainly, it is the responsibility of our training programs to ensure that this does not occur.

The second issue is that of mental health promotion and illness prevention. Currently, it is fashionable to speak about the efficacy of mental health promotion and primary prevention of mental illness. Initiatives in which these concepts seem to be the driving forces for program development and resource allocation are underway at local, provincial, and federal levels. Unfortunately, many of these initiatives are based on a overly simplistic concept of psychiatric disorder (often arising from the paradigm of infectious disease); there is a dearth of well-thought-out and clearly quantifiable evidence as to the efficacy of promotion and prevention in significantly reducing the incidence or prevalence of major mental illness. Instead, there seems to be a firmly held notion that promoting “mental health” would significantly decrease the incidence and prevalence of “mental illness.” Furthermore, there seems to be an overly enthusiastic promotion of a view that identifies “primary prevention” as the panacea to the problems of mental illness. The sad truth is that, at this time, we know little about the pathoetiology of most mental illnesses, and what we do know suggests that (as Drs Goldbloom and Garfinkel have pointed out) the pathogenetic factors are likely to be multiple. A relative weighting of these factors and the environmental conditions in which they express themselves differs from disorder to disorder. The bottom line is that we currently have insufficient evidence to support an enthusiastic and uncritical embracement of promotion and primary prevention methods as a panacea to mental illness.

By contrast, there is ample evidence to indicate that secondary preventive measures, properly applied, can be both effective and cost-efficient. Secondary preventive measures are designed to decrease the prevalence of psychiatric disorder and its associated morbidity in the community. Given our knowledge base at this time, it is essential that while we try to identify further the potential value of promotion and prevention in mental illness, we focus our energies and resources on secondary preventive models. Furthermore, we have a responsibility to provide our trainees with the best possible tools with which to engage in these activities. These tools are and will continue to be sophisticated diagnoses; comprehensive, early, and effective intervention; systematic evaluation of outcomes; and the dissemination of this information to the community outside the universities’ walls.
In my opinion, it is necessary for psychiatric training programs to address these issues. In the future we will need to focus not only on the training of psychiatrists but also on the critical discussion of these concepts in the community as well.

Reference


Stan Kutcher, MD, FRCPC
Halifax, Nova Scotia

Re: Impulsivity, Defensive Functioning, and Borderline Personality Disorder

Dear Sir:

I read with interest the article, “Impulsivity, Defensive Functioning, and Borderline Personality Disorder” by Dr van Reekum and colleagues (1).

Recent methods of evaluating impulsivity have incorporated cognitive dimensions of evaluation (2). While evaluating personality and mood factors, the authors did not report on cognitive measures of impulsivity. Examining these factors might give a more comprehensive evaluation of impulsivity and increase the range of possible cognitive and pharmacological interventions (3,4).

References


Laurence Jerome, MBChB, MRCPsych, FRCPC
London, Ontario

Author Acknowledged

Dear Sir:

As principal author on the article entitled “Clozapine: Current Status and Role in the Pharmacotherapy of Schizophrenia” (1), I would like to note that Dr Michael Teehan from Dalhousie University in Halifax, Nova Scotia, should be added as an author to this publication. He contributed to this manuscript from its outset, and the omission of his name from the list of authors was an oversight on my part.

Reference


Gary Remington, MD, PhD, FRCPC
Toronto, Ontario

Re: Clozapine—Current Status and Role in the Pharmacotherapy of Schizophrenia

Dear Sir:

I read with interest the article by Remington and others (1) on the current status and role of clozapine in the pharmacotherapy of schizophrenia. Approximately one-third of patients with schizophrenia resistant to conventional neuroleptics show a favourable response to clozapine.

There is emerging literature that clozapine is at least as effective in the treatment of certain forms of refractory bipolar disorder such as the manic phase of schizoaffective disorder and dysphoric mania. The evidence for its efficacy comes largely from open trials. Nonetheless, the results are significant because a large number of these mood-disordered patients had been refractory to trials of various pharmacologic agents including mood stabilizers used in combination (2,3).

Clozapine is currently indicated only in those patients with schizophrenia who are either intolerant of or unresponsive to antipsychotic drugs. While controlled trials of clozapine in patients with refractory mood disorders are urgently needed, such patients should not be denied the benefit of having the drug paid for by the government-funded programs. The course of illness in certain patients who suffer from severe, psychotic mood disorders is indistinguishable from that of schizophrenia and is often marked by significant functional impairment and even cognitive deterioration (4).

References


Verinder Sharma, MB, BS, FRCPC
London, Ontario
Dear Sir:

Frontal lobe dysfunction is widely suspected to underlie negative symptoms of schizophrenia (1). There is a possible correlation between hypodopaminergic function in the prefrontal cortex and negative symptoms of schizophrenia. The antidopaminergic effect of typical neuroleptics in the frontal lobe has been considered a causal factor for neuroleptic-induced deficit syndrome (2). By contrast, the superiority of clozapine in the treatment of negative symptoms has been partially explained by its ability to enhance the dopamine release from neurons projecting to the prefrontal cortex (3).

Studies evaluating the use of dopamine agonists in the treatment of schizophrenia have shown some efficacy for these drugs. Some patients have shown improvement after coadministration of dextroamphetamine and haloperidol (4), for example. Further support is derived from a strong correlation between the level of dopamine metabolite in the cerebrospinal fluid and the prefrontal activity during Wisconsin Card Sorting Test performance (5).

To the best of my knowledge, no previous study or report has been published to evaluate the effects of coadministration of dopamine agonist with clozapine in the management of treatment-resistant schizophrenic patients.

I wish to report on a patient who demonstrated a rapid and significant improvement of negative symptoms in response to the addition of bromocriptine (to treat pituitary adenoma) after 6 months of unsuccessful treatment with clozapine.

A 42-year-old woman had been physically and mentally well until the age of 22, when she developed symptoms suggestive of schizophrenia, undifferentiated type. She had been frequently admitted to the hospital for adjustment of medication. Her pharmacotherapy trial was typical—lithium augmentation and benzodiazepine agents—but the improvement was limited to the positive symptoms. For this reason, a regimen of clozapine was started (600 mg divided doses) despite adjuvant selective serotonin reuptake inhibitor (SSRI) (fluoxetine 20 mg daily). The patient completed the first 6 months on this regimen with no changes and started to experience galactorrhea and amenorrhea during the latter part of clozapine trial. Serum prolactin level was 190 mg/L. Magnetic resonance imaging showed an enlarged sella turcica and small, asymmetrical soft tissue enlargement with no suprasellar extension. There were no other intracranial abnormalities. She was diagnosed as having a case of pituitary adenoma.

Treatment for the pituitary adenoma was started with bromocriptine at 2.5 mg bid and increased to 5 mg bid after one week. Three weeks later the patient and her family reported a significant improvement in her self-care, and she was more spontaneous, alert, and organized. Her facial expression reflected a broad range of appropriate affect. She also remained free of any positive symptomatology. Her prolactin level was 30 mg/L.

Clozapine is often more effective than typical antipsychotics in treating treatment-resistant schizophrenia. Almost one-half of patients with inadequate neuroleptic responses received greater benefit from clozapine (6). Patients with the negative subtype of schizophrenia, however, were found to be less responsive to clozapine than patients with the positive subtype of schizophrenia (6). Some researchers recommend discontinuation of clozapine if the improvement is not achieved in the first several months (6), while other investigators assert that clozapine’s ability to suppress psychopathology may be delayed until the sixth to ninth month of treatment in a significant number of patients (7).

Our patient showed no improvement in negative symptomatology after 6 months on a therapeutic dose of clozapine (600 mg) or with adjuvant SSRI. She demonstrated significant improvement in negative symptomatology after coadministration of bromocriptine, however, which had been added for the initial purpose of treating her pituitary adenoma. This clinical finding is consistent with a previous study that confirmed a reduction in dopamine turnover in the negative subtype of schizophrenia (5,8). It is also consistent with pharmacodynamic studies of the mechanism of action of clozapine. Besides its antagonistic effect on a variety of receptors (for example, 5-HT\textsubscript{2a}, 5-HT\textsubscript{2c}, 5-HT\textsubscript{3a}, α-adrenergic receptors, histamine H\textsubscript{1}, muscarinic, and D\textsubscript{1}, D\textsubscript{2}, and D\textsubscript{3} receptors [7]), it has been suggested that the antidopaminergic effect of clozapine is anatomically site-specific, that is, active in the mesolimbic dopamine system and absent in the nigrostriated dopamine system, with possible enhancement of dopamine turnover in the toberoinfundibular tract (9). This profile makes it the most suitable antipsychotic in patients with concomitant pituitary adenoma. It has also been suggested that clozapine enhances selective increase in the output of dopamine neurons projecting to the prefrontal cortex (3).

When clozapine is ineffective in alleviating negative symptomatology, there is some justification for adding a dopaminergic agent as adjuvant therapy. It is important to note that the risk of provocation of positive symptoms appears to be very low. Small doses of clozapine (25 to 50 mg/day) have been used successfully in bromocriptine- or levodopa-induced psychoses (10).

The conclusion is that an adjunctive dopaminergic agent can be very efficacious for the negative symptoms of schizophrenia that do not respond to clozapine alone. Further study of this agent as adjunctive therapy to clozapine should use a
Swelling of Salivary Glands with Clozapine Treatment

Dear Sir:

Clozapine, an atypical antipsychotic effective in the treatment of traditional neuroleptic-resistant and/or neuroleptic-intolerant schizophrenic patients (1,2), has a different profile of side effects than standard antipsychotics (3,4). One of the most common is sialorrhea, occurring in around 23% of cases (3–5). Rare cases of salivary gland swelling have been cited, with or without hypersalivation, near the start of clozapine treatment, following a dosage increase (6–8). This case report describes transient swelling of the left submandibular salivary gland in a patient on stable clozapine treatment for 13 months.

Mr D, aged 44, met DSM-IV (9) criteria for disorganized schizophrenia. He underwent various neuroleptic treatments at different dosages with no significant improvement. Immediately prior to clozapine, he was taking a daily oral dose of haloperidol 6 mg and clordesmetildiazepam 8 mg. When put on clozapine (maximum dosage: 400 mg/day), the psychotic symptoms improved partially, but 13 months into treatment, the patient developed monolateral swelling in the left submandibular gland. There was no tenderness at palpation, but the surrounding lymph glands were swollen. The patient was afebrile, and no leukocytosis appeared. The erythrocyte sedimentation rate was slightly affected (21: normal range 1 to 15 mm/h). Four days into antibiotic and antiinflammatory treatment, clinical symptoms resolved. Specific laboratory research (amylase, isoamylase, lipase levels) carried out 10 days after resolution showed normal results.

The most common causes of salivary gland swelling—benign or malignant salivary gland neoplasm, chronic sialadenitis (single gland), or bacterial infection (10)—were ruled out because of the absence of clinical symptoms or laboratory findings characteristic of those conditions. To our knowledge, there are 6 published cases that have attributed salivary gland swelling to clozapine. It is noteworthy that the swelling in the reported cases, as opposed to our case, usually occurred in females. An additional difference was the appearance, in our case, of the adverse reaction long after treatment was started and with no dosage increase.

The current pathogenetic hypothesis links this side effect to the anticholinergic properties of clozapine that cause a stasis of saliva, encouraging precipitation of calcium salts and formation of a small calculus, which obstructs the duct leading from the gland (8). The stasis of saliva, further worsened by the calculus-induced blockage, induces distension of the duct and irritation of the surrounding area (11). In approximately 50 patients treated with clozapine, we found only one case of salivary gland swelling. It is probable, as Vasile and Steingard (8) suggested, that those patients particularly susceptible to anticholinergic effects of clozapine on salivary glands suffer swelling. In our patient, this side effect did not result in discomfort serious enough to warrant clozapine withdrawal, a step recommended only in cases of severe inflammation or high fever (8).

We feel that, in this case, the late onset of swelling is compatible with the pathogenetic hypothesis suggested by Vasile and Steingard (8), since the stasis of saliva related to clozapine’s anticholinergic properties continues to occur, even if partial tolerance develops over time.

The objective of this case report is to communicate possible salivary gland swelling, even after a long period of treatment with clozapine or with no dosage increase.

References

Dear Sir:

In a patient for whom multiple sclerosis (MS) has not been diagnosed, psychiatric disorders may be attributed to other causes (1–5). We encountered a 52-year-old black male whose family brought him to the hospital and reported that he had developed confusion, loose associations, and a precipitous deterioration in his social interactions and self-care. One month earlier he experienced another episode of psychosis that was attributed to the death of a friend. Because of this psychosocial stressor, he was given a diagnosis of brief reactive psychosis, which resolved. Other medical history included systemic hypertension, congestive heart failure, and noninsulin-dependent diabetes mellitus.

Vital signs showed hypertension, normal temperature, tachycardia, and tachypnea. The neck showed jugular venous distention. Rales were audible over the lung fields. The heart’s point of maximum impulse was displaced, and a third heart sound was heard. There was pitting edema of the legs. The neurologic examination showed no localizing signs. Electrocardiogram revealed atrial fibrillation and biventricular enlargement. Chest X-ray showed pleural effusions and cardiomegaly.

Treatment of heart failure was initiated with the expectation that the patient’s mental status would improve as he stabilized. His respiratory status deteriorated, however, and he died on the third hospital day.

An autopsy revealed death to be due to pulmonary emboli from the deep veins of the legs. The brain showed multiple, plaque-like lesions deep in the white matter. Microscopic sections of these areas showed demyelination and coalescence of plaques. These neuropathologic findings established the presence of MS.

Occult MS may have been related to the patient’s psychotic episodes. Psychosis in MS is uncommon but well documented (1–8). Psychosis or other psychiatric disorders generally develop in patients with known disease (9–14); psychosis as a presenting feature of previously undiagnosed MS is unusual (1–5). Among such patients, psychotic behaviour apparently developed independently, although in some patients there may have been previous psychiatric disorders. Disorientation and deterioration in self-care and social interactions were common presentations among these patients. Other presentations included common psychotic features such as bizarre behaviour (1–4), hallucinations (2,4,10), and psychomotor disturbances (3,4) or unique features such as hyperreligiosity (1), paranoia (10), and hypersexuality (5).

The possible psychiatric manifestation of MS in this patient educated us to be wary of a recurring psychosis to which different etiologies are ascribed and encouraged us to consider MS in the differential diagnosis of psychosis.

References

Dear Sir:

I would like to describe the appearance of withdrawal symptoms (which, to my knowledge, have not yet been reported) after discontinuation of venlafaxine, a 5-HT-Norepinephrine (NE) reuptake inhibitor antidepressant.

Mr A, a 26-year-old man, had a 12-year history of dysthymic disorder with atypical features and social phobia. He had been treated with psychotherapy for more than 10 years without success.

On examination, his prominent symptoms were hypersomnia, fatigue, mental slowing, lack of concentration, and reduced functioning.

Treatment was started with fluoxetine, 20 mg/day, to which desipramine, 50 mg/day, and lithium, 600 mg/day, were later added. Because 8 weeks later only a partial response was observed, these medications were discontinued, without adverse effects, and venlafaxine, 150 mg/day, was started. After 4 weeks of therapy, no significant positive effect was observed, so venlafaxine was abruptly discontinued with the aim of trying a new antidepressant.

The day after the discontinuation of venlafaxine, the patient noted the appearance of brief “bursts” of dizziness, which lasted for a few seconds and occurred numerous times throughout the day. He had never before had such symptoms. They were associated with headache, nausea, fatigue, insomnia, sweating, and worsening of depression. These symptoms worsened during the following 2 days. Then, considering these symptoms a withdrawal reaction, the treating physician restarted venlafaxine, 75 mg/day. Symptoms disappeared the next day and did not return during the following gradual tapering of the drug beginning a week thereafter.

The symptoms observed in this case after abrupt discontinuation of venlafaxine are similar to those reported after withdrawal of selective serotonin reuptake inhibitors (SSRIs) (1,2). SSRI withdrawal symptoms include dizziness (of the kind observed in this case [2]), vertigo, headache, nausea, vomiting, diarrhea, myalgia, fatigue, insomnia, irritability, sweating, and anxiety.

Because venlafaxine is a 5-HT-NE reuptake inhibitor, it is expected to have withdrawal features in common with SSRIs, apart from a similar side effect profile.

The close temporal relationship between sudden discontinuation of venlafaxine and appearance of symptoms similar to the SSRI withdrawal syndrome (as well as their disappearance soon after reintroduction of venlafaxine) suggests that these symptoms were a withdrawal reaction and not the result of a depressive relapse.

Venlafaxine discontinuation should be done gradually to reduce the probability of inducing a withdrawal syndrome.

It is noteworthy that this patient did not develop withdrawal symptoms after fluoxetine discontinuation, suggesting that serotonin reuptake inhibitors may differ in their ability to cause withdrawal reactions. This might be related to individual sensitivity, drug half-life, 5-HT reuptake inhibition potency, dose, rate of tapering, and individual variations of metabolism.

References