Letters to the Editor

Re: Late-Onset Neutropenia With Clozapine

Dear Editor:

The recent case report by Thompson and colleagues on late-onset neutropenia with clozapine raises a few questions (1). The authors do not define mild neutropenia and incorrectly call an absolute neutrophil count (ANC) of 1.86 x 10^9/L mild neutropenia. The most accepted definition of mild neutropenia is an ANC of 1.0 to 1.5 x 10^9/L (2). Further, the authors do not elaborate on the role of valproic acid in the presentation of clozapine-induced neutropenia. Valproic acid is independently associated with neutropenia (3). In addition, a case report describes a patient on a combination of sodium valproate and clozapine who developed a potentially serious drop in white cell and neutrophil counts that reversed on discontinuation of valproate (4). On the basis of this report, the investigators recommended that consideration should be given to stopping sodium valproate before the thresholds are reached for the discontinuation of clozapine. Clozapine-induced neutropenia is much more common than agranulocytosis (cumulative incidence of 2.7% and 0.73%, respectively) (5), which means that a substantial proportion of patients experiencing neutropenia with clozapine treatment do not progress to agranulocytosis. Transient or benign neutropenia not progressing to agranulocytosis has been described in the literature, and some patients with mild neutropenia have been shown to do well on continued treatment with clozapine (6). It has been suggested that drug interaction may be responsible for neutropenia in clozapine-treated patients and that clozapine need not necessarily be discontinued (7). Given that clozapine is administered to treatment-resistant patients, balancing potential side effects like agranulocytosis and clinical deterioration assumes greater significance, especially in patients developing mild neutropenia while taking other medications with a potential to cause neutropenia. Thus it would have been interesting to see whether this patient’s neutropenia would have resolved had the valproic acid been discontinued. Nevertheless, this report highlights the need for future research to explore alternate options when treating clozapine-induced mild neutropenia while continuing clozapine and also to devise means to differentiate benign neutropenia from neutropenia progressing to agranulocytosis.

References

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Reply: Late-Onset Neutropenia With Clozapine

Dear Editor:

We appreciate the opportunity to respond to Dr Duggal and Dr Singh, and we welcome their comments. We agree with their observation that an accepted strict definition of mild neutropenia is an absolute neutrophil count of 1.0 to 1.5 x 10^9/L. We used the term mild neutropenia to reflect the neutrophil count being designated within the “amber” range as defined by the Clozaril Patient Management System (1). This designation prompts the need for biweekly blood draws.

We are aware that the role of concomitant valproic acid needs to be considered, given the evidence that it can cause direct bone marrow suppression producing blood dyscrasias including neutropenia (2).

In this case, there was no evidence of neutropenia with valproic acid prior to the institution of clozapine. Further, cessation of the clozapine alone resulted in a gradual resolution of the neutropenia, which was sustained, to our knowledge, for at least 2 years and despite the addition of risperidone and the patient’s remaining on valproic acid.

With hindsight, it might have been worthwhile to discontinue the valproic acid prior to being forced to cease the clozapine. However, the history of a grand mal seizure would argue against ceasing the valproic acid in the first instance.

Thankfully, in this particular scenario, the patient’s symptoms responded satisfactorily to risperidone, with the added benefit of less onerous hematological surveillance.

It is an important issue to consider when a patient has failed trials with other atypical medication, necessitating administration of clozapine. In such a situation, premature cessation of clozapine may result in clinical deterioration.

References
We would then agree that a judicious trial off valproic acid in the first instance would be warranted.

The issue of the role of drug interaction in producing the late-onset neutropenia is interesting, pertinent, and needs further delineation. We accept the suggestion that a complex interaction between valproic acid and clozapine, and perhaps some other clinically undetected factor, lowered the threshold for a clozapine-induced neutropenia that might not have progressed to agranulocytosis. Certainly, Gerson has suggested that the mechanism of toxicity in most patients with neutropenia who do not progress to agranulocytosis is distinct from that responsible for agranulocytosis (3).

The case report cited by Dr Duggal and Dr Singh appears to exemplify this situation (4): reversible neutropenia was temporally related to the addition of other medication in a patient taking both clozapine and valproic acid.

We believe that our report and the valuable comments of Dr Duggal and Dr Singh should prompt further investigation into the etiology of mild neutropenia in the context of clozapine use. We encourage future researchers who have the access and opportunity to explore carefully the burgeoning databases on clozapine patients—in particular, to tease out factors associated with this clinically relevant phenomenon with respect to the role of drug interaction and to delineate factors that may determine the outcome of the neutropenia.

References


Kenneth G Orr, MBBS, FRANZCP
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Re: Characteristics of Methylphenidate in a University Student Sample

Dear Editor:

The article entitled “Characteristics of Methylphenidate in a University Student Sample,” by Barrett and others, was quite interesting and highly informative (1).

There have been several studies regarding methylphenidate abuse in university settings, especially in the US; however, very little about statistics regarding intranasal and intravenous use are present in the literature. The statistics about intranasal and intravenous use are highly important in light of the dramatic rise in methylphenidate abuse in the last 15 years.

Several studies have shown that there are similarities between cocaine and methylphenidate in their ability to block dopamine transporters, especially when taken intravenously. Some researchers postulated that the shorter effects of cocaine might account for its potential to be heavily abused (2).

A similar study done at the University of Michigan by Teter and others (3), in which a sample of 2250 students was studied, appears consistent with Volkow and others. The interesting finding, though, was that 79% of those who abuse methylphenidate started taking it during college, while 19% started in high school. Methylphenidate users accounted for only 2% of the students studied.

Other US college surveys have shown much higher prevalence. A survey at the University of Pennsylvania showed that almost 9% of undergraduates used someone else’s prescription medications, most of which were methylphenidates. Another survey showed that 16% of students at a small liberal arts college reported having tried methylphenidate recreationally and that 12.7% reported having taken it intranasally. A more recent survey in 2002 involving students at the University of Florida showed that 1.5% used ritalin recreationally in the 30 days prior to the study (4).

Barrett and others mentioned that prescription diversion was the primary source of methylphenidate use in this sample; however, other sources are prevalent. Methylphenidate is one of the 10 most frequently stolen controlled medications, although this may not necessarily be the case regarding college students. The popularity of the drug among college students could also be attributed to the competitive nature of colleges. The drug has been linked with some students’ desire to excel in a competitive academic environment, because it helps them to stay focused through periods of fatigue.

Several studies have reported how best to curb methylphenidate abuse. In addition to the suggestion put forth by Barrett and others, other researchers have suggested methods such as alternative pharmaceutical delivery systems that are not easily manipulated for injection or inhalation and the use of centralized prescription databases. We believe education would be one of the most effective ways to address this problem in a university setting, especially if, as suggested by Barrett and others, prescription diversion is a major source of access to methylphenidate. Education would be helpful in cases where only the person given the prescription, and not whoever eventually abuses the drug, is advised of the risks and benefits.
References

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Reply: Characteristics of Methylphenidate in a University Student Sample

Dear Editor:

We thank Dr Oyemade and Dr Patel for their comments on our article. As these authors point out, methylphenidate misuse among college students appears to be a widespread phenomenon, and strategies are clearly needed to curb the inappropriate use of this prescription medication. Although studies that have examined prevalence of methylphenidate misuse among college students have reported variable rates across institutions (2% to 16%), these findings are difficult to interpret, owing to relatively modest levels of participation among those invited to participate (ranging from 20% to 64%) (1,2). Nevertheless, a recent study examining past-year illicit prescription stimulant use across 119 American colleges from geographically diverse regions documented stimulant medication misuse in over 83% of the institutions examined (3). This suggests that the inappropriate use of methylphenidate is a widespread problem.

We also agree with Dr Oyemade and Dr Patel’s suggestion that the competitive nature of colleges might contribute to the propensity for methylphenidate abuse in college students. In our sample, 30% of those who reported inappropriately using methylphenidate reported doing so exclusively for study. Although we did not systematically record all possible motives for methylphenidate use among recreational users, several of these participants spontaneously reported the use of methylphenidate for both recreational and study purposes. In addition to the competitive scholastic pressures facing many college students, there are also numerous reports of high rates of binge drinking and drug experimentation among college students (4,5), and this too might contribute to their propensity to misuse methylphenidate. Anecdotal evidence suggests that many college students may deliberately mix methylphenidate and alcohol to prolong their drinking sessions (6) or to achieve desirable subjective effects (7). In our study, alcohol-methylphenidate mixing was reported as a relatively common practice among recreational users.

Given that illicit methylphenidate may be in high demand for multiple reasons in a college setting and given the potential social stigma involved with taking psychiatric medications (8), individuals with legitimate prescriptions for methylphenidate may experience considerable pressure to divert their medication as a means of belonging. Moreover, because many college students may live away from home, their prescription adherence is unlikely to be closely monitored. While we agree with Dr Oyemade and Dr Patel that increased education is likely key to curbing the problem of prescription diversion, such efforts might prove most effective if directed toward physicians, pharmacists, and patients alike.

References

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Problem Gambling in the Canadian North

Neglected

Dear Editor:

Dr Cox and others (1) should be commended for paying close attention to the rapidly rising mental and social health issues of problem gambling. I do, however, have several comments.

One is the unacknowledged limit of the study, which is described as a “national survey” of Canada. The survey, however, covered only the 10 provinces. While the research community’s marginalization of the Territories is not uncommon enough to warrant a letter, I think there is a significant risk that an article like this will lead to further neglect of the significant problem of gambling in the Territories. This neglect is particularly remarkable as the
authors seem to forcefully argue that the presence of casinos and video lottery terminals (VLTs) may contribute to increased problem gambling. The fact that the Territories typically lack both may lead one to think there is no problem there. The observed reality is quite the contrary. During my 2.5 years working on Baffin Island as a psychiatrist, I heard many stories from patients, social workers, and colleagues on how gambling has created tremendous rifts in families, ruined relationships and careers, and contributed to violence and suicide. My very informal survey, using a hastily translated Inuktitut South Oaks Gambling Screen, with the staff at a social service agency showed that everyone knew someone (or more) with a “problem.” In a typical Baffin Island town of 500 people, there were generally 2 or 3 gambling gatherings every night, more on weekends and paydays. Heavy betting with snowmobiles, entire monthly salaries, and grocery monies was common. This form of socialization, turned into problem gambling, is particularly remarkable because many towns have banned alcohol; thus, people rely on gambling for entertainment. My educated guess is that problem gambling on Baffin Island, for example, is far above the reported “national” average of 2.0%. On the part of the community at large, there was a tremendous wish and hope to address this mental and social health issue. I think researchers like Dr Cox and others can greatly contribute to this much-neglected area.

The study’s emphasis on forms of commercialized gambling as predictors of problem gambling is also problematic. Although the authors acknowledge that the study is a macroanalysis of available data and propose future studies to include more longitudinal and relational issues regarding VLTs, I think more sophisticated research would include such factors as cultural attitudes toward gambling, different forms of gambling, the local meaning of gambling, and geographical determinants of gambling. For example, the game of patik is a vastly popular, relatively culturally accepted, socially attractive form of gambling for the Baffin Inuit (in addition to bingo and lottery tickets). This fast-paced card game—akin to gin and rummy and often involving intense betting—is at the root of many Inuit gambling problems. This issue will never be recognized if future studies are narrowly city and commercially focused.

Reference


Reply: Problem Gambling in the Canadian North Neglected

Dear Editor: We thank Dr Law for his thoughtful letter, and we welcome the opportunity to reply. Our first point is that there was no a priori research decision to exclude the Territories. Rather, our focus on the 10 provinces reflected the sampling design of Statistics Canada’s Canadian Community Health Survey: Mental Health and Well-Being (CCHS 1.2). In a description of the survey design, an early Statistics Canada report stated that the CCHS 1.2 target population did not include “those living in the three territories, on Indian Reserves and Crown lands, clientele of institutions . . . and residents of some remote areas” (1). This sampling design was reiterated in a recent special issue of the Canadian Journal of Psychiatry, where it was nevertheless stated that the CCHS 1.2 “constitutes a comprehensive source of information on the mental health of Canadians” and that it does so at the “provincial and national levels” (2). Finally, Statistics Canada authors have also emphasized that the CCHS 1.2 “offers first-time information on problem or pathological gambling across Canada” (3). We used language to stress that we were interested in interprovincial comparisons because this is where the recent widespread increase in legalized gambling activities in Canada has occurred.

Our second point is that our primary research focus was an examination of the prevalence rates of problem gambling in different regions of the country in the wake of the introduction of newer forms of gambling (VLTs and casinos) and their availability in Canadian communities. As Dr Law points out, there are no VLTs or permanent casinos in the Territories.

It has often been said that gambling has existed in almost all cultures throughout history, and Dr Law offers some informative examples from Inuit communities. We agree with Dr Law that a national research agenda on gambling should eventually include all communities in Canada. However, it is the potentially harmful effects of the widespread introduction and ease of availability of the newer forms of legalized gambling activity that have been of particular concern to Canadian public health experts (4).

References


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