Dear Editor:

The following case history may appear anecdotal, but it nevertheless sheds some light on an aspect of treating acute mania. Mrs WP, aged 69 years, was admitted to the psychiatric unit of our hospital with symptoms consistent with acute mania. She exhibit grandiose ideation, euphoria, psychomotor excitement, flight of ideas, and pressure of speech. She also exhibited overt sexual acts, such as running nude in the unit. This patient has a long history of bipolar affective disorder type 1, and she has been followed up in the community. According to the history gathered, she was receiving gabapentin 300 mg 3 times daily, to which she became noncompliant.

While in the hospital, she showed no insight and felt that there was nothing wrong. She wanted to walk nude, arguing that there are nude beaches in the world, and therefore, nudity should be acceptable in the psychiatric unit. She refused to take any medication, again claiming that there was nothing wrong with her. She became hostile, and I had to use intramuscular benzodiazepine treatment. Her Young Mania Rating Scale (YMRS) score was 48, which is consistent with severe mania. She was started back on gabapentin and also received risperidone liquid 1 mg twice daily. After 2 doses of risperidone, which were administered within a couple of days and with only 2 doses. Given this case report, it may be wise to consider risperidone liquid as a first choice in the case of acute mania, in addition to any other mood stabilizer.

TM Abraham, MD, FRCP
Welland, Ontario

Methylphenidate and the Cytochrome P450 System

Dear Editor:

I reviewed with interest the case report in your journal describing unexpected grand mal seizures in a 14-year-old boy treated for attention-deficit hyperactivity disorder (ADHD) with methylphenidate (MPH) 60 mg daily, to which bupropion was added (1). The author notes, “it is also possible that the risk of seizures was amplified by the combination of bupropion and methylphenidate” (1, p 790).

This case report is of concern, insofar as a combination of bupropion and MPH, if known to be safe, would be a sensible augmented regimen for treatment-resistant or treatment-refractory cases of ADHD (2) and perhaps even depressive disorders (3).

However, the literature suggests a mechanism for possible deleterious interaction between these 2 agents; namely, it is possible that MPH inhibits a hepatic isoenzyme that contributes to the metabolic clearance of bupropion from the body. Several authors have alluded to methylphenidate’s capacity to inhibit the degradation of cyclic antidepressants (4–6). MPH has been cited as an inhibitor of CYP2D6 (7). It may also inhibit other hepatic enzymes, including perhaps CYP2B6, the isoenzyme predominantly responsible for the metabolism of bupropion (8), or other enzymes not currently known to help clear bupropion.

The net result of such a possible interaction could be higher bupropion plasma levels and greater risk of seizure. This risk may be compounded by bupropion’s own inherently greater epileptogenic potential and the rapidity of its time to peak levels in both the older formulation and the newer slow release (SR) compound (9). It has been theorized that “rapidity of dose escalation” is a factor in the capacity for antidepressants to cause seizure (10). Peak plasma level occurs within 2 hours for bupropion (traditional preparation) and within 3 hours for the newer SR preparation after oral ingestion. This is 2 to 3 times faster than, for example, “time to peak plasma level” for fluoxetine, which requires 6 to 8 hours (9). By reducing metabolic clearance, a concomitantly administered hepatic enzyme inhibitor such as MPH may accelerate time to peak and also amplify peak plasma concentrations, both of which have been implicated as risks in bupropion-induced seizures (10).

References

Replied: Methylphenidate and the Cytochrome P450 System

Dear Editor:

I thank Dr Baird for his valuable comments. Indeed, it has been confirmed that CYP2B6 is the principal enzyme involved in the hydroxylation of bupropion (1). Reports regarding the effect of methylphenidate (MPH) on the cytochrome P450 (CYP450) system are sparse, and to date, inhibition of CYP2B6 by MPH remains unproven. However, in vitro MPH inhibition of CYP2D1 and CYP2D has been demonstrated (2), and animal studies have shown inhibition of CYP1A, CYP2E1, and CYP3A by MPH (3). I agree with Dr Baird’s suggestion that other isozymes of the CYP450 system may also be affected by MPH; nevertheless, scientific evidence endorsing this hypothesis is not yet available.

Further studies are necessary to define the possible drug interactions of MPH with drugs metabolized by CYP450.

With the information available, we can prudently state that clinical practice requires caution when coadministering MPH and bupropion, as well as when combining MPH with other medications that are CYP450 substrates.

References


Abel Ickowicz MD, FRCP
Toronto, Ontario

Antiaggressive Action of Combined Risperidone and Quetiapine in a Patient With Schizophrenia

Dear Editor:

Aggressive and hostile behaviours can be manifestations of schizophrenia, among other mental disorders (for example, mood disorders and dementia) (1) and contribute considerably to institutionalization (2). In patients with chronic schizophrenia, clozapine treatment has resulted in a selective improvement in aggressive behaviour, beyond the global improvement shown on the Brief Psychiatric Rating Scale (BPRS) (3,4), although this improvement did not necessarily extend to the positive symptoms of psychosis (5). Risperidone treatment showed a greater selective effect on hostility in schizophrenia patients than did haloperidol or placebo (6), although there are some contradictory data from an open trial comparing risperidone and haloperidol (7). In clinical practice, risperidone has proven very useful in treating aggression and violence in patients with chronic refractory schizophrenia (8). In a case series, olanzapine had better, but not significantly different, tranquilizing properties after 3 days of treatment, compared with haloperidol (9). Quetiapine in high dosages (up to 900 mg daily) was used successfully in 2 treatment-resistant patients with schizophrenia and concomitant aggression (10,11). In the first instance, quetiapine was added to divalproex sodium (10), and in the second, it was coadministered with risperidone (11).

In this report, we describe the case of a patient with an unremitting acute psychotic episode whose hostility and aggressive symptoms improved soon after he was given combined quetiapine and risperidone.

Case Report

A 35-year-old, unmarried man was involuntarily admitted to our clinic. He showed auditory hallucinations, delusions of persecution and reference, aggressiveness, psychomotor agitation, and restricted affect. He appeared markedly dishevelled. His score on the Brief Psychiatric Rating Scale (BPRS), in which each item is rated 1 to 7, was 57; on tension, hostility, and agitation he had a score of 6 (severe). His psychiatric problems started about 3 years ago, when he stopped working and showed total social isolation, wandering, and untriggered and unpredictable verbal outbursts. He refused any psychiatric treatment and was diagnosed with schizophrenia, paranoid type, according to DSM-IV criteria.

He refused medication and was therefore given haloperidol 30 mg daily intramuscularly for 5 days. When he subsequently consented to take medication, risperidone was gradually added while the dosage of haloperidol was slowly tapered. After 20 days, his regimen consisted only of risperidone 12 mg daily. However, he did not show any sign of improvement, and any effort to stop restraint failed. As a result, after 1 week of risperidone monotherapy, quetiapine was added and titrated to 500 mg daily in 5-day intervals. When he was evaluated 1 week later, he showed marked improvement in symptoms, scoring 36 on the BPRS; on hostility and tension, he scored 2 (very mild), and on agitation, 3 (mild). After about 40 days of hospitalization the patient was released from restriction, and 2 weeks later, he was discharged from our clinic. His risperidone was decreased to 8 mg daily; no change was made in his daily quetiapine dosage. One month after discharge, his clinical state remains the same, with no

Can J Psychiatry, Vol 48, No 6, July 2003
deterioration or improvement (BPRS score, 33); however, he exhibits no further aggressive or hostile behaviour. For the first time in 3 years, he visited his workplace, and he is planning to resume working.

Discussion
In our patient, aggression, hostility, and agitation were controlled in a very short time after he was given combined risperidone and quetiapine. A major factor of the superior therapeutic effects of atypical antipsychotics is 5-HT2A receptor blockade. Through this action, atypical antipsychotics may regulate prefrontal and limbic dopamine release during cognitive activity and stress. Some data also indicate that certain atypical antipsychotic drugs (clozapine, quetiapine, and ziprasidone) have important 5-HT1A receptor agonist properties (12). These effects of atypical antipsychotics may contribute to their antiaggressive action, because central serotonin deficit and prefrontal, as well as limbic system, dysfunction has been associated with aggressive behaviour (1). However, no conclusive remarks can be made for the antiaggressive action of quetiapine as monotherapy or combination therapy until more systematic studies appear in the literature.

References

Vasillis P Bozikas, MD, PhD; Charoula Deseri, MD; Stergios Pitsavas, MD, PhD; Athanasios Karavatos MD, PhD
Thessaloniki, Greece

Ultrarapid Response to an Antidepressant: A Clue to Bipolarity?

Dear Editor:

I have noted that patients referred for treatment-resistant depression often report episodes of response to an antidepressant within a few days, with subsequent loss of efficacy. Reflecting the literature (1,2), in recent years I have had an increasing index of suspicion for bipolarity among these patients. I observe an association between a history of ultrarapid response to antidepressant medication and the reporting of symptoms eventually recognized as compatible with bipolarity. A recent review of the spectrum of bipolar illness by Ghaemi, Ko, and Goodwin included a table (3, p 129) that did not, however, mention such a possible association. A search of the literature (specifically, Medline, using the key words antidepressant, depression and drug therapy, bipolar, and time factors; and PsychNFO, using the key words bipolar disorder, major depression, antidepressant drugs, and onset of action) failed to elicit any data related to this association. I undertook to examine a series of cases. These included 8 patients naturally referred and treated in a cognitive-behavioural therapy group for patients with bipolar disorder (BD) and 6 patients consecutively referred for consultation and subsequently diagnosed with BD. I assessed these patients further, using the Mood Disorders Questionnaire (MDQ) (4). The MDQ confirmed a history of hypomania or mania, and several additional written questions were asked, including the following: “What is the least time it (the antidepressant) took to work after you started (in days)?” and “When did this most rapid response occur?” (among previous trials of antidepressant therapy). The cohort ranged in age from 24 to 48 years (average age 39.8 years). There were 8 women and 6 men. Their diagnoses according to DSM-IV-TR criteria (7) were as follows: BD I (n = 4), BD II (n = 7), and BD not otherwise specified (NOS) (n = 3).

Of the patients, 13/14 (93%) reported a therapeutic response to antidepressants at some time; 10/13 (77%) reported responding in 3 days’ time or less, at some time. The other subjects’ shortest response times were reported as 21, 10, and 7 days, respectively. The average response time was 4.4 days. Of the 11 patients reporting a response in 7 days or less, 9 (82%) had that ultrarapid response early in their course (that is, during the first or second trial). Of 14 subjects, 13 (93%) reported becoming agitated at some time in response to an antidepressant.

These findings suggest a very strong association between retrospectively reported ultrarapid response to antidepressants and bipolarity. Although retrospective data are subject to more flaws than prospective data, an examination of the longitudinal course of recurrent affective illness at the National Institutes of Mental Health showed a high correlation between retrospective “life chart” data and data gathered prospectively (5). In this series, most patients did not have a diagnosis of BD I, and the female-to-male ratio did not quite reflect the higher
Developmental Alcohol Exposure, Circadian Rhythms, and Mood Disorders

Dear Editor:

Alcohol exposure during rapid brain growth causes cell loss, alters connections between brain regions, and decreases the production of brain chemicals responsible for the communication among neurons (1,2). Thus, it is reasonable to suggest that alcohol may adversely affect the development of the suprachiasmatic nucleus (SCN), the master circadian pacemaker. Adult rats exposed to alcohol during the early postnatal period—a critical period of brain development—exhibited a shortened circadian sleep–wake cycle (1). Other experimental and clinical studies have reported that prenatal exposure to alcohol results in sleep abnormalities (1,3).

Studies suggest that abnormalities in circadian rhythm are involved in the etiopathogenesis of seasonal affective disorder (SAD) (4,5). The phase-delay hypothesis of SAD postulates that some components of circadian rhythm are phase delayed relative to sleep in SAD. The photoperiod hypothesis of SAD suggests that the shortening of the photoperiodic environment during winter months triggers SAD. Some researchers have proposed that the pathophysiology of SAD is related to the changes in strength or precision of circadian rhythms. Abnormalities of circadian rhythm have also been implicated in the etiopathogenesis of nonseasonal mood disorders (5–7). The temporal distribution of rapid eye movement (REM) sleep earlier in the night in depression patients could be a result of a phase advance of circadian rhythms. Several clinical features of bipolar disorder, such as diurnal mood variation, early morning awakening, and the cyclical pattern of relapse, may be associated with circadian disruption (6). Several types of experiments indicate that alterations in the timing of sleep and wakefulness relative to other circadian rhythms may trigger the onset or offset of episodes of depression and mania (6,7).

Thus, it is reasonable to suggest that developmental alcohol exposure produces abnormalities in circadian rhythms that may contribute to the development of seasonal and nonseasonal mood disorders. Circadian rhythm abnormalities are one of many harmful effects of developmental alcohol exposure.

References


Leo Sher, MD
New York, New York

Attentionnementsexuelspratiqués par un adolescent substitué en testostérone

Cher Editeur:

Les anabolisants stéroïdiens sont des médicaments utilisés depuis plus de cinquante ans dans le traitement de nombreuses maladies organiques, dans la contraception masculine mais aussi, autrefois, dans certaines pathologies psychiatriques (1). Plus récemment, des athlètes les ont utilisés pour développer leurs capacités musculaires. Ce nouvel attrait a entraîné aux E.-U. une explosion de la consommation de ces médicaments

References

qui touche non seulement les athlètes mais aussi les lycéens non sportifs (2).

Ce cas clinique rapporte l’apparition de troubles du comportement sexuel chez un adolescent qui souffre d’une insuffisance anté-hypophysaire congénitale substituée en testostérone, et qui se présente spontanément à la consultation alors qu’il fait l’objet d’une inculpation pour des attouchements sexuels sur mineurs.

Fils de médecins, M. X. a eu une enfance et une scolarité sans problème. Son histoire est liée à son déficit hormonal qui a motivé depuis sa toute petite enfance des traitements et des consultations régulières en compagnie de sa mère. 13 ans, son endocrinologue a décidé le déclenchement de sa puberté par l’administration de testostérone (heptylate de testostérone, une injection toutes les semaines). Le patient rapporte avoir alors ressenti une modification de son caractère : agressivité, érections incontrôlées, quasi permanentes, associées à une excitation sexuelle. Ainsi, il s’est mis à demander à son petit frère de lui faire régulièrement des attouchements sexuels pendant tout le temps de la prescription.

A 18 ans, gardant des enfants, il a récidivé sur une petite fille. Ce sont les parents de cette dernière qui ont porté plainte et occasionné la révélation de l’ensemble des troubles, ce qui a entraîné une inculpation et un arrêt de l’heptylate de testostérone pour l’instauration d’un traitement par testostérone undécanoate (1 comprimé par jour).

Le patient est venu spontanément à la consultation pour rechercher un soutien psychologique face à la dureté et la longueur des mesures judiciaires.

L’examen clinique révèle un jeune homme ne présentant ni pathologie psychiatrique, ni trouble de la personnalité apparent. Il s’agit d’une personne calme au fonctionnement opératoire, un peu immature, sans vie sexuelle en dehors des faits incriminés et ayant une difficulté à exprimer des émotions. Il a vécu le changement de traitement comme une libération de cette tension sexuelle incontrôlable, aliénante. Depuis, il dit être soulagé de la disparition totale des troubles qu’il attribue à la testostérone. Il est conscient de ses actes et est impatiente du jugement afin de purger sa peine.

Dans le cadre du contrôle judiciaire, le patient vient scrupuleusement et régulièrement à la consultation depuis plus de 5 ans. Il n’a jamais montré le moindre trouble psychiatrique ni le moindre élément révélateur d’un comportement transgressif. Il n’a jamais cherché de bénéfice secondaire à ce travail qui est resté privé.

Au cours de cette période, il est passé progressivement, malgré ses craintes, de un à trois comprimés de Pantestone, ce qui constitue une dose plus optima pour la prévention du risque d’ostéoporose, sans qu’aucun trouble ne resurgisse. Il s’est aussi intéressé de plus près à sa maladie en participant notamment à un programme de recherche.

Cette observation met de l’avant un trouble du comportement sexuel apparaissant au moment de l’instauration d’un traitement hormonal à un âge où la sexualité est en cours de construction, et disparaisant à l’arrêt de ce traitement, sans que l’on retrouve un terrain prédisposant ni un trouble psychiatrique. Le traitement est conforme aux bonnes pratiques en vigueur (3). L’imputabilité de l’heptylate de testostérone est forte au regard de l’anamnèse et compte tenu du contexte de la collecte des données : un cadre psychothérapeutique où le patient s’est présenté librement sans recherche de bénéfice secondaire. De plus, d’après le patient, les troubles ont totalement disparu après le changement de traitement, sans aucune raison pharmacologique explicable ou connue avec un recul de presque 3 ans.

Les anabolisants stéroïdiens ont une action psychotrope connue. Différentes études animales ont montré leur effet sur le comportement agressif, sexuel mais aussi de dominance (1). Ils ont été impliqués dans certains troubles du comportement violents ou agressifs chez des sportifs de dopant (4,5). En revanche, il n’existe aucun cas semblable en pharmacovigilance et dans la littérature chez un adolescent substitué. Ce cas clinique incite à avoir une vigilance particulière chez des adolescents substitués.

Bibliographie


Jean-Christophe Seznec
Le Kremlin Bicêtre, France

Dichotomization and Manipulation of Numbers

Dear Editor:

With reference to Dr Streiner’s article (1), I agree that numerical data should not usually be dichotomized, but researchers should actively choose numbers that reflect clinical or scientific reality (2), and there may be good reasons for dichotomizing or otherwise manipulating data. (To maintain validity of the hypothesis testing, a decision to manipulate the numbers must be taken before seeing them!)

I offer some examples of situations wherein manipulation of numbers is appropriate:

1. Caseness. Dr Streiner considers the possibility that there is a qualitative difference between people suffering and those not suffering from depression and that this “caseness” is what chiefly interests us. He proposes that a reasonable cut-point on the Beck Depression

Letters to the Editor

Can J Psychiatry, Vol 48, No 6, July 2003
Inventory (BDI) is 15/16. If we take the (unusual) view that caseness, not BDI score, is affected by independent variables and may in turn affect other variables (that is, effects are direct and not via BDI score), we should dichotomize.

2. Floor and ceiling. Streiner offers the following example: “Within the range of low income (up to, say, $10 000 a year), the actual dollar amount is unimportant, insofar as it buffers against stress, while above a certain amount ($60 000, for example), more money doesn’t provide more protection. Within the middle range, however, we may suspect that there is a linear relation” (1). I suggest that the appropriate treatment of this variable is to recode amounts below $10 000 to $10 000 and amounts above $60 000 to $60 000.

3. Pathology at both extremes. Sometimes there is a healthy range, and there is a linear relation” (1). I suggest that the appropriate treatment of this variable is to recode amounts below $10 000 to $10 000 and amounts above $60 000 to $60 000.

With regard to this discussion, I should like to note several points. First, after manipulation, numbers will often not satisfy the mathematical assumptions required for some statistical tests. However, randomization (permutation) tests are widely accepted and are readily available in such software as StatXact (3). Assumptions of normality and equality of variances are then unnecessary. We calculate the statistic of interest for our data (for example, the difference between the means). Then, by assigning the observations randomly to the groups, we get a computer to repeatedly generate artificial datasets and calculate the statistic of interest, thereby obtaining a null distribution of this statistic. Some of the well-known nonparametric or rank tests are based on this philosophy, but with critical values determined theoretically rather than by computer simulation.

The second point of note is this: in contrast to the caseness example above, it may be that independent variables which change the BDI in 2 people from (say) 30 to 25, or from 15 to 10, are also likely to change the caseness of other people, moving them from “depressed” to “not depressed.” For example, the factors may act on the mean of the continuous variable, with caseness being a consequence. Dichotomization would then foolishly discard information. Thus, with such variables, researchers need to decide whether caseness or the score is the reality, because it affects whether dichotomization is appropriate.

The third point to note is that, if a psychological or medical test results in a number, we may be tempted to perform mathematical operations such as subtraction and averaging. However, we are then implying that a change from 30 to 25 (say) equates to a change from 15 to 10. Do we really know this? Further, do we know whether 3 patients having 5%, 50%, and 95% stenosis is equally as desirable as their having 50%, 50%, and 50% stenosis? (If we average, we lose the distinction between these situations.) I doubt that such questions have been answered, even about such widely used measures as the BDI and percentage stenosis. A recent example of the issue (4) is that the relation between pain intensity and its interference with function may be nonlinear: a reduction of pain intensity from 7 to 4 might be considered more beneficial and more clinically relevant than a reduction from 4 to 1.

In summary, researchers should worry about whether their dependent variable truly represents what is of interest. However, if using a randomization test, they do not need to worry about mathematical assumptions.

References

T Paul Hutchinson, PhD
Sydney, Australia

Reply: Dichotomization and Manipulation of Numbers

Dear Editor:

Dr Hutchinson is quite correct that we need not worry about the assumptions of parametric tests (for example, t-tests, analyses of variance, and related techniques) if we use randomization tests. However, I believe that his recommendations to recode data when there are floor or ceiling effects, or pathology at both extremes of a variable, misses the mark. First, recoding does not eliminate the problem; it only masks it. If a scale has a floor (or ceiling) effect, it means that it is not accurately tapping the attribute in question. People may have less (or more) of whatever is being measured, but the scale is unable to differentiate among them, owing to insufficient items at the extremes. It is a tenet of psychometric theory that reliability is directly related to a scale’s ability to discriminate among people (1). Recoding values does not solve the problem of unreliability at the extremes; it merely disguises it by assuming that all people below the floor (or above the ceiling) actually have the same score.

The second problem is that recoding may distort any relation between or among variables. Recoding and randomization tests may be able to answer the question of statistical significance, but they do not help us understand these relations and may even change them. If we retain the original values, then we are able to use other techniques, such as nonlinear regression, to better model what is going on.

Hutchinson is absolutely correct, though, to caution researchers to be concerned about whether their dependent variable truly represents what is of interest. Scores on a test are simply scores on a test; they are not reality.

References

David L Streiner, PhD, CPsych
Toronto, Ontario