Dear Editor:

Dr David Streiner impressively demonstrates that statistical power is lost if variables measured along a continuous scale are converted into categorical variables (1). He observes that the categorization of a continuous variable is justified only if the data are markedly skewed or if the variable shows a nonlinear relation with another variable.

I suggest that there is one more situation in which continuous variables are better categorized: when the values obtained are “guessstimates.” In India, for example, many patients who belong to lower socioeconomic strata, and some rural patients, do not know their exact age. They provide approximations that are usually a multiple of 5, and thus, a data set might contain a large number of patients aged 30, 35, or 40 years. When using such data, it may make more sense to analyze age as a categorical variable. Expressed otherwise, it might be a good idea to categorize continuous variables when there is reason to believe that the variable cannot be, or has not been, accurately measured.

Reference


Chittaranjan Adrade, MD
Bangalore, India

A Case of Neuroleptic Malignant Syndrome With Clozapine and Risperidone

Dear Editor:

Neuroleptic malignant syndrome (NMS) occurring with the use of atypical neuroleptics has been described (1). Only a single case of NMS occurring with concomitant use of clozapine and risperidone has been reported (2). We report a case suggesting NMS after risperidone was added to clozapine therapy. We explore the differences between these 2 cases and discuss the safety of combining clozapine and risperidone.

Case Report

Mr R, aged 30 years, was diagnosed with paranoid schizophrenia at age 10 years. Despite risperidone treatment, psychotic symptoms recrudesced, he was rehospitalized, and risperidone was optimized to 6 mg daily without side effects. However, no improvement occurred, and risperidone was stopped. Consecutive olanzapine and piperazine monotherapies did not lead to any improvement. A clozapine regimen was started and increased to 750 mg daily over 22 months. This was well tolerated.

Four months later, the patient was still suffering from psychosis, and risperidone was added. After a further 3 months, he displayed only minor improvement. His risperidone was increased to 1 mg in the morning and 2 mg at bedtime for 2 days, and then to 2 mg twice daily. On day 5 of the risperidone treatment, the patient developed a low grade fever (38.5°C), tachycardia, and delirium. He presented a slight rigidity of the limbs. We suspected NMS and stopped neuroleptics. Creatinine kinase (CK) levels increased on day 6 (248 U/L) and rose to 1671 U/L on day 9.

Mr R improved rapidly: his fever, tachycardia, and delirium resolved less than 48 hours after neuroleptics were stopped. CK returned to normal on day 16. Rechallenge of clozapine monotherapy on day 16 was well tolerated, and his paranoid symptoms improved considerably.

Hasan and Buckley insist on the diagnostic confusion between NMS and neurotoxicity secondary to the use of neuroleptics, especially in polypharmacy (1). However, despite the restricted clinical picture of our case, NMS is the most probable diagnosis. When we quickly stopped medication, the symptoms abated immediately. There is no evidence to exclude a neurotoxicity secondary to bitherapy with risperidone and clozapine. Our case lies in the middle of a continuum with clearly defined NMS at one end and suspicion of NMS at the other.

In another reported case, the risperidone dosage was 16 mg daily (2); in our case, it was 4 mg daily. In the former case, the patient did not tolerate the dosage, and precursor signs of NMS were observed before clozapine was added. This points to risperidone as the causative agent. In the case of our patient, both risperidone and clozapine were well tolerated in monotherapy. Tyson and others report interaction between risperidone and clozapine (3), and we believe that the addition of risperidone could have reduced clozapine metabolism. This would have increased the risk of NMS caused by neuroleptic bitherapies and also by a simultaneous augmentation of clozapine levels. (Unfortunately, clozapine levels were not available.) The fact that risperidone and clozapine monotherapies were well tolerated in our case points to the interaction itself as a causative factor. These data support Tyson and others’ suggestion that clozapine blood levels should be monitored when it is combined with risperidone.

References

Zonisamide Treatment of Bipolar Disorder: A Case Report

As far back as 1971, carbamezapine was used to treat acute mania (1). In 1995, the FDA approved divalproex sodium for the treatment of patients presenting with acute mania. Over the last few years, newer anticonvulsants have been used to treat bipolar disorder (BD); these include gabapentin, lamotrigine, oxcarbazepine, and topiramate (2). In March 2000, the FDA approved zonisamide—a drug chemically unrelated to other anticonvulsants (3)—for the treatment of partial seizures in adults. I present a case in which a patient with BD was tried on numerous conventional mood-stabilizing agents and stabilized on zonisamide. I believe this to be the first reported case since zonisamide’s release in the US.

Case Report

Mr A, aged 51 years, has a 27-year history of BD type I. His most recent episode was hypomanic. His illness significantly impaired him over the years, and he had multiple hospitalizations. Over the years, he took various medications, including lithium, carbamezapine, gabapentin, valproic acid, haloperidol, thioridazine, bupropion, fluoxetine, and nortriptyline. On initial presentation, Mr A was taking a combination of venlafaxine extended release (XR) 300 mg daily, mirtazapine 60 mg daily, quetiapine 200 mg daily, and topiramate 100 mg twice daily. His depressive symptoms with concomitant anxiety had stabilized over a 5-month period. He began to experience hypomanic symptoms, scoring 17 on the Young Mania Rating Scale (YMRS) (4), despite increasing his topiramate to 200 mg twice daily. An adjunct mood stabilizer, zonisamide was added at a dosage of 100 mg daily, with the patient giving informed consent for this off-label use. Zonisamide was increased by 100 mg after 2 weeks. At the end of 1 month, the patient was taking 300 mg daily, and his YMRS score was 3. Initially, he experienced sedation but otherwise tolerated the addition of zonisamide without problems. After stabilization, his zonisamide plasma level was 13.8 ug/ml. The topiramate was tapered off over 1 month, with no adverse effects. At 4 months, Mr A remains stable.

Zonisamide has been commercially available in Japan since 1989. It has been studied in an open-label, add-on fashion in the treatment of patients with acute mania. In this group, 33% of patients with bipolar mania showed remarkable improvement, while 80% of patients with BD had more-than-moderate global improvement (5). Zonisamide is a 1,2-benzenoxazole-3-methanesulfonamide chemically distinct from other antiepileptic agents (6). It has several mechanisms of action: it blocks sensitive sodium channels and T-type calcium channels, it scavenges hydroxyl and nitric oxide radicals, and it enhances dopamine function (7). It also has GABAergic properties (2) and is reported to be structurally similar to serotonin (5). The prescribing information does not give recommendations for monitoring zonisamide, nor does it give a therapeutic range (3). Lepke and others determined that patients taking between 100 and 400 mg daily had plasma levels ranging from 7 to 40 ug/ml, with the mean ranging from 13 to 20 ug/ml (8). Zonisamide may prove to be a valuable addition to the ever-growing number of mood stabilizing agents used to treat BD, but it needs more controlled study. A case report exists of zonisamide-induced mania. The Ann Pharmacother 2002;36:119–29.


Timothy R Berigan, DDS, MD
Tucson, Arizona

Combined Use of Atypical Antipsychotics and Cognitive-Behavioural Therapy in Schizophrenia

Dear Editor:

There are few reports of cognitive-behavioural therapy (CBT) combined with atypical antipsychotic drugs (AAs) in cases of treatment-resistant schizophrenia, especially from North America (1,2). Given that AAs improve cognitive function (3), it would be interesting to explore whether AAs complement CBT and whether they can potentiate the effect of CBT. I discuss these issues in the case of a patient with treatment-resistant schizophrenia who was given clozapine and risperidone along with CBT.

Case Report

Mr C, aged 29 years, was diagnosed with paranoid schizophrenia of 9 years’ duration. He suffered from auditory hallucinations, somatic passivity, and delusions of persecution, reference, and control. As formally tested, he had poor attention span and impaired verbal working memory. His baseline score on the Positive and Negative Syndrome Scale (PANSS) was 129. Having failed conventional AAs, Mr C was started on clozapine,
dresed by CBT (2). Interestingly, cloza-
dealt with. These difficulties are ad-
don, specific thought-content difficul-
ties are improved by AAs (3). Sec-
tive, specific thought-content difficul-
ties and possibly influenced the self-rating
scores. These study findings, however,
and reaction time, while risperidone im-
proves memory and concept formation
(3).
It may also be speculated that AAs po-
tentiate CBT. CBT in part reduces symp-
tomatology by decreasing the salience of
old learning and involving new, alterna-
tive appraisals, which requires intact
learning processes; risperidone and ola-
napine improve memory function, in-
cluding new learning (3,7). Further
validation of these observations in a sys-
tematic study comparing combined
treatment with AAs alone is encouraged.

Two months of this combined therapy
saw Mr C’s PANSS score dropping to 59
(reduced by 54% from intake). His cog-
nitive functioning, including attention,
memory, and judgement, also improved.
Notably, after starting CBT, his convic-
tion regarding his delusions decreased,
as did his preoccupation with somatic
passivity and auditory hallucinations.

The CBT was then shifted to once-
monthly sessions, and the patient main-
tained this improvement at his last
follow-up, 6 months later.

This report underscores the effectiveness
of combined pharmacotherapy and psy-
chotherapy in managing treatment-
resistant schizophrenia, especially for
patients in whom an initial good re-
sponse to clozapine is curtailed by subse-
quent clozapine-induced seizures.
Although it might be difficult to segre-
gate the individual effects of AAs and
CBT, these 2 modalities may be comple-
mentary, especially because they both
bring about cognitive rehabilitation in
patients with schizophrenia. The realm of
cognitive rehabilitation includes 2
general components (6). First, specific
deficits in attention, cognitive flexibility,
and vigilance must be treated. These
deficits are improved by AAs (3). Sec-
ond, specific thought-content difficul-
ties, such as hallucinations, delusions,
and medication compliance, must be
dealt with. These difficulties are ad-
ressed by CBT (2). Interestingly, clo-
zapine and risperidone may in turn be
complementary in improving cognitive
deficits: clozapine improves attention
and reaction time, while risperidone im-
proves memory and concept formation
(3).

Daily self-rating forms that record symp-
toms and severity are widely used to con-
firm the diagnosis of PMS or PMDD, but
there are no specific questionnaires to
measure psychosocial functioning in
PMDD (7). Therefore, we studied levels of
distress, degrees of impairment, and
impact on lifestyle in women with
PMDD, compared with a control group.
We used 3 validated self-rating scales:
the Symptom Questionnaire (SQ) (8),
the Sheehan Disability Scale (9), and
the Quality of Life Enjoyment and Satis-
faction Questionnaire (Q-LES-Q) Short
Form (10) as applied to premenstrual
symptoms. Subjects diagnosed with
PMDD (n = 15) and control subjects (n = 15)
gave written informed consent and
completed the self-rating questionnaires
(once only) during the luteal phase. They
also reported general demographic data
and menstrual history. We conducted in-
dependent t-tests to determine the effect
of PMDD as measured by the self-rating
scales; preliminary findings show sig-
ificant between-group differences in
the mean total scores of distress levels,
functional impairment, and quality of
life.

Our study results indicate that women
with PMDD report more distress and im-
pairment and less satisfaction during the
luteal phase, compared with the control
subjects. However, these results should be
viewed with caution, because there
were few participants, the questionnaires
were only completed once, and the meas-
ures were not designed specifically for
PMDD. The study also did not take into
account unusual current stressors that
might have magnified symptom severity
and possibly influenced the self-rating
scores. These study findings, however,
do suggest that the impact of PMDD on

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Harpreet S Duggal, MD
Pittsburgh, Pennsylvania

Distress Levels in Patients
With Premenstrual Dysphoric
Disorder

Dear Editor:

It is estimated that 75% of women of re-
productive age experience premenstrual
syndrome (PMS) (1), which includes emo-
tional, physical, and behavioural
changes. However, only 3% to 8% expe-
rience premenstrual dysphoric disorder
(PMDD) (2)—severe premenstrual
mood symptoms that interfere with nor-
mal daily functioning (work, social
activities, and relationships) (3). The
chronological relation of symptoms and
the menstrual cycle has been investi-
gated (4), as have been medications and
lifestyle modifications for PMS and
PMDD (2). The effect of medication on
psychosocial functioning in PMDD pa-
tients has also been evaluated (5,6), but
few studies have systematically looked
at the impact of symptoms on lifestyle
daily functioning in subjects with
PMDD, compared with control subjects
(7).

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Disorder

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Daily self-rating forms that record symp-
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Our study results indicate that women
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were only completed once, and the meas-
ures were not designed specifically for
PMDD. The study also did not take into
account unusual current stressors that
might have magnified symptom severity
and possibly influenced the self-rating
scores. These study findings, however,
do suggest that the impact of PMDD on
psychosocial functioning can be measured systematically by self-rating questionnaires. The preliminary results of the SQ support the view that mood symptoms, and not physical symptoms, characterize women with PMDD (2) and that there is a correlation between psychosocial functioning and the mood symptoms (4) measured by these 3 questionnaires.

Prospective daily charting of symptoms is crucial to establish the diagnosis of PMDD, but measuring psychosocial functioning may also help to confirm severity and assist in treatment recommendations (for example, medication, lifestyle changes, or alternative therapies). We encourage a larger study using accepted, standardized ratings of psychosocial functioning in relation to PMDD.

Alcoholism, Seasonal Depression, and Suicidal Behaviour

Dear Editor:

Several studies in different countries have reported a high prevalence of alcohol-use disorders among people who commit suicide (for example, 56% in New York [1] and 43% in Northern Ireland [2]). Such figures far exceed the prevalence of alcohol-use disorders in the general population (3,4). Because comorbid alcoholism and depression are associated with increased suicidality (5), global suicide prevention strategies should include a focus on alcohol-use disorders that aggressively treats comorbid depression (3).

Seasonal affective disorder (SAD), a condition wherein depressions in fall and winter alternate with periods of no depression in the spring and summer, is one of the most treatable causes of suicidal behaviour. Further, recent data suggest that seasonal depression is closely related to alcoholism (6,7), and some patients with alcoholism have a seasonal pattern to their alcohol abuse. These patients may be self-medicating SAD with alcohol. Family studies also suggest a relation between alcoholism and SAD (7,8). It has been proposed that if some patients with alcoholism attempt to self-medicate SAD with alcohol, or if SAD predisposes this population to alcohol relapse, then treatment of SAD with light therapy may help to prevent alcohol relapse (7). Although suicidal ideation occurs less frequently in patients with SAD than in those with non-seasonal depression (9), suicidal ideas are nonetheless commonly found in this population (9). SAD can be effectively treated with light therapy that relieves suicidal ideation, consistent with overall clinical improvement. Thus, light therapy for patients with SAD might both decrease suicidal ideation and prevent relapse into alcoholism. Worsening suicidal ideation is uncommon in patients treated with morning light therapy. However, clinicians should always be vigilant for symptoms of suicidality. In addition, pharmacologic and psychological treatments can help SAD patients who abuse alcohol. Contemporary treatment may prevent suicidal behaviour in patients with comorbid SAD and alcoholism.

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Dear Editor:

Two recent publications describe the shrinking number of medical students who choose psychiatry (1) or, specifically, child psychiatry (2) as a career and review potential reasons for this decrease. I would like to describe a program that seems to interest students in the rewards of a career in psychiatry. This summer program is offered to students following their first or second year of medical school. This program provides a paid, 8-week clinical experience. All students who...
apply for the 3 available positions are interviewed. Selection is based upon interest in a career in one of these specialties demonstrated by past successful involvement with children and adolescents, confirmed through reference checks.

There are 3 parts to the experience. First, students are given an extensive list of opportunities to learn about children with developmental disabilities or psychiatric disorders, or both, and also to learn about the various professionals in the multidisciplinary teams who work with these children. They are asked to take advantage of as many of these opportunities as possible and to keep a diary of their experience. In weekly meetings with the coordinator, the diaries are reviewed to ensure that students are engaged in a broad experience. The second requirement is a weekly case presentation. Students interview a child, review the file, and speak to other involved professionals. Over the course of the summer, students are expected to present 1 case from each residential clinical unit, so that by the end of the experience they have personally seen a range of problems. The final requirement is that students individually or collectively present a topic of interest at medical rounds or another suitable formal occasion. The students have an opportunity to write up a case under the direction of a medical geneticist and to do an original research project, medical peer assessment, or program evaluation project. This generally forms the basis of their presentation.

To date, of the participating students who have entered or submitted applications to enter postgraduate training \((n=10)\), 5 have enrolled in family medicine, and 5 have enrolled in psychiatry or pediatrics. (By contrast, when our program focused upon service delivery, there was no pattern to the summer students’ postgraduate training choice.) The students choosing family medicine are interested in rural practice and have indicated in interview that they will need more training in these areas than is available in the basic curriculum. We continue to follow up on the summer students who have not yet declared their postgraduate training choice.

References


Greta Toni Swart, PhD, MD, FRCPC
London, Ontario

A Case of Paroxetine-Induced Galactorrhea

Dear Editor:

We report a case of galactorrhea in a 24-year-old woman (Ms N) voluntarily admitted for depression and anxiety. Paxil 10 mg taken orally once daily was prescribed, and on treatment day 5, Ms N developed galactorrhea (the nonpupillary discharge of milk-containing fluid from the breast). This patient had no history of galactorrhea. She first noticed the discharge on the night of treatment day 5 and described it as grey-creamy (right nipple) and white-creamy (left nipple). The volume was significant enough that discharge dripped down her abdomen and flanks. She did not notice any bloody, greenish, or foul-smelling discharge. The medication was discontinued the next morning, and the discharge ceased that night.

In our approach to this patient, we sought to eliminate the most likely causes of galactorrhea. Hypothyroidism results in increased levels of thyrotropin-releasing hormone, which increases prolactin secretion. Kidneys clear prolactin, and thus, kidney disease may cause secondary hyperprolactinemia. During pregnancy, and for up to 2 years after cessation of breast-feeding, galactorrhea may be a normal finding. Because Ms N’s routine admission measurements of urea, creatinine, thyroid-stimulating hormone, and beta human chorionic gonadotropin (b-HCG) were all normal, we were able to eliminate underlying kidney disease, hypothyroidism, or pregnancy as possible causes of galactorrhea.

Serum prolactin measurements taken the day that galactorrhea began and 3 days after it subsided were both within normal range. Thus, we did not observe a drug-related increase in prolactin, and we could reassure the patient that she did not have a pituitary adenoma. When evaluating prolactin measurements in cases of galactorrhea, it must be remembered that prolactin is necessary but not sufficient to initiate lactation, and milk production may continue in the presence of normal basal plasma prolactin levels.

Clinicians should be aware of the possibility that selective serotonin reuptake inhibitors (SSRIs) can induce galactorrhea. This case report can be added to others (1,2), as well as to the manufacturer’s databases (3). The approach to patients should comprise discontinuation of the implicated SSRI, careful documentation of the galactorrhea, and documentation of recent menstrual history. Pregnancy testing and assessment of thyroid status should be done where menstrual history is equivocal or hypothyroidism is a possibility. Assessing prolactin level is likely to be low yield; it should be undertaken where clinically indicated or where there is significant patient anxiety. In cases of nonresolving galactorrhea, clinicians should direct their attention to neoplastic, structural, metabolic, and other causes, as described in Pena and Rosenfeld’s recent comprehensive review (4).

References

Beyond Principal-Component Analysis of the Positive and Negative Syndrome Scale in Patients With Schizophrenia

Dear Editor:

Cancel and others (1) add their study of Positive and Negative Syndrome Scale (PANSS)-rated symptoms of schizophrenia to the growing literature indicating that 5 symptom factors are necessary to account for symptoms of the disorder. They note many similarities in the items contained in each factor across studies but also allude to several differences that may be related to the study sample’s clinical characteristics. Other possible reasons for differences in factor composition may be related to sample size and to the limitations of the principal-component method. Indeed, principal-component factor analysis is recognized as an exploratory method. We wish to bring attention to our large-scale, multicentre study of the PANSS factor structure. In it, we use the more rigorous method of confirmatory factor analysis (2). In a sample of 1233 subjects with schizophrenia, we found that groups varying widely in age, chronicity, and illness phase did not significantly differ in their symptom structure. We identified a 5-factor structural model of the PANSS that met statistical criteria for good model fit. The criterion of good fit is an index of the degree of correspondence between the order in sample data and in the proposed model. Our model used 25 of the 30 PANSS items, organized into 5 factors: negative, positive, activation, dysphoric mood, and autistic preoccupation. Although identification of a good-fit model establishes the model’s internal consistency, validity studies are necessary to demonstrate model utility. The model’s discriminant validity has been demonstrated in a study of sex differences in the relation of homelessness to symptom severity (3), in a study of symptom differences between familial and deficit-syndrome schizophrenia (4), and in a study of the association between symptoms and cognitive-perceptual deficits in schizophrenia (5). Symptom subscales based upon this model have been published, as have tables of norms based upon an adult population with chronic schizophrenia (6).

References


Leonard White, PhD
West Brentwood, New York
Lewis A Opler, MD, PhD
Mount Vernon, New York

Olanzapine-Induced Hair Loss

Dear Editor:

Olanzapine (Zyprexa Zydis) 5 mg daily was initiated in hospital, and the dosage was increased to 15 mg daily over the subsequent 4 weeks. Within 2 weeks of starting olanzapine, at 7.5 to 10 mg daily, she reported gradually increasing hair loss. The hair loss accelerated when the daily dosage was increased to 15 mg. She complained of losing a handful of hair after washing or brushing it, and often found her pillow and bed sheet covered with hair in the morning. Although there was no hair count, the hair loss was obviously distressing her and was witnessed by the treatment team.

The patient continued to express delusional beliefs, and we suspected noncompliance when nursing staff noted the patient vigorously brushing her tongue shortly after taking the Zydex wafer. This was confirmed when her serum olanzapine concentration was found to be 35 nmol/L (at 10 mg taken orally daily, the average level is reported to be 74 nmol/L [1]). Because the patient did not improve and was distressed by the side effect, we switched olanzapine to risperidone over a 1-week period. As the olanzapine dosage was reduced with the addition of risperidone, the patient reported decreased hair loss. Noncompliance to oral medications remained a problem, and she was eventually switched to flupenthixol depot, with no further complaint of hair loss. The patient was not taking any other medications prior to admission, and olanzapine was the only medication she was taking during the period of hair loss. She was otherwise healthy and had no concurrent toxicity associated with its use; that is, hair loss.

A 41-year-old Asian woman was admitted to hospital with a 5-year history of bizarre behaviour and erotomaniac and persecutory delusions. She believed that her ex-employer was pursuing her and harassing her with messages sent via television and radio because she refused to engage in a relationship. She also believed that he had bribed her coworkers and tenants with 1 million dollars to harass her and cause water damage to her rental property.

Letters to the Editor
medical conditions. Her thyroid-stimulating hormone level was 1.32 mU/L (normal is 0.5 to 5 mU/L). We did not identify any other potential cause of hair loss. Trichillomania was ruled out by the treating psychiatrist.

Drug-induced alopecia involves an interruption of hair growth when the hair follicles prematurely enter into the telagen (resting) phase (2,3). Spontaneous, diffuse hair loss generally occurs within 3 months of initiating therapy; it is usually reversible upon discontinuation of the offending drug (2,3). Several psychotropic medications have been implicated—most commonly, valproic acid and lithium. Rarely, antidepressants (including tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], and nefazodone) are implicated (4–7). There is a single case of hair loss reported with haloperidol (8), but none are reported with atypical neuroleptics. To our knowledge, this is the first case report of hair loss associated with olanzapine therapy.

There are a few reported cases of alopecia secondary to olanzapine in the database from Eli Lilly Canada Inc, with an estimated incidence of less than 0.01% (M Bain, personal communication, 2001). The cellular mechanism of hair loss by olanzapine or psychotropic drugs is not known. One hypothesis is that these medications chelate zinc and selenium, which are believed to be crucial to hair growth. However, the efficacy of routine zinc and selenium supplementation remains unconfirmed. Dosage reduction or drug discontinuation generally results in complete resolution. Noncompliance, owing to poor insight or adverse effects, is a major concern in the psychiatric population. Olanzapine is generally considered to be well tolerated, but clinicians should recognize that this rare but distressing side effect can lead to poor compliance, as occurred in this case.

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Marianna Leung, BSc Pharm, BCPP
Katherine Wrixon, MD, FRCP
Ronald A Remick, MD, FRCP

Vancouver, British Columbia

Paternal Age as a Risk Factor

Dear Editor:

Recent research reports have focused attention on the association between advanced paternal age and increased risk of schizophrenia in offspring (1,2). In addition to schizophrenia, numerous genetic illnesses are reported to have the same association with increased paternal age (3). An increased mutation rate related to increased paternal age has been documented in the male gametogenesis (4). Most of these illnesses are autosomal-dominant disorders (5). Two x-linked recessive illnesses—hemophilia A and Lesch-Nyhan disease—have been frequently found with increased maternal grandpaternal age (6–8). It is proposed that the origin of schizophrenia can in some cases be related to a mutation in the gametogenesis of the father that is related to aging. It is further proposed that, as with hemophilia A and Lesch-Nyhan disease, the mutated gene or genes in some cases of schizophrenia and other genetic illnesses can be transmitted to future generations. In such cases, the illness could be expressed in a distant relative far removed in time from the original mutational event. Further genetic research on germline mutations related to paternal age is needed to establish the significance of paternal age as a risk factor.

References

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