Letters to the Editor

Massive Weight Gain and Hostility Force Mirtazapine Stoppage

Dear Editor:

Mirtazapine is a novel antidepressant with a mechanism that involves enhancing serotonergic and noradrenergic neurotransmission via blockade of alpha-2 adrenergic autoreceptors and heteroreceptors. Because of its unique pharmacologic profile, it is devoid of anticholinergic-, adrenergic-, and serotonin-related side effects (1). The most frequently reported side effects are mild and transient sedation and weight gain (1,2). Others have found it to have substantially better tolerability than the serotonergic or tricyclic antidepressants (3,4). I report the case of a patient who stopped mirtazapine after severe and unusual side effects.

Case Report

Ms KD is a 40-year-old nurse with a long history of unipolar depression that resulted in several hospitalizations and several antidepressant trials, including electroconvulsive therapy. During one such episode, her depression was treated unsuccessfully with adequate trials of citalopram, venlafaxine, paroxetine, and bupropion. After a washout period of about 10 days, Ms KD was started on 15 mg of mirtazapine given at bedtime. After a week, this was increased to 30 mg. She also took 0.5 mg of lorazepam up to twice daily. She remained depressed, became irritable, and noticed significant swelling of her hands, legs, feet, and eyelids. She became incapacitated because the swelling prevented grasping and turning faucets, and she became unable to get in and out of the bathtub. Climbing stairs became impossible, and she needed help with most activities. Ms KD also became extremely anxious and very hostile, especially toward her 2 children. She became fearful at night and asked her husband to be close to her, preventing him from watching television. All these new problems—and especially her hatred of her own children—frightened her, and she requested that mirtazapine be discontinued. Shortly thereafter her hostility and fear subsided, the edema resolved, and her weight gradually returned to baseline. Subsequently, she has been doing well on clomipramine.

Even though mirtazapine has been reported to be well tolerated and to have potential value as a treatment for anxiety disorders (5,6), my patient became more anxious and hostile. The weight gain of 40 lb was also much higher than reported in the literature. This case underlines the need for clinicians to be alert to the possibility of severe idiosyncratic adverse events in patients starting newer products.

References


G Abraham, MD, FRCP
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Functional Dyspepsia and Mirtazapine

Dear Editor:

Functional dyspepsia (FD), also known as nonulcer dyspepsia or dyspepsia of unknown cause, refers to a complex of symptoms characterized by pain or discomfort and bloating centred in the upper abdomen, early satiety, fullness, and nausea. These upper gastrointestinal symptoms are not associated with any structural abnormality demonstrable by standard diagnostic investigations (that is, radiological, endoscopic, and histological). There is no evidence that dyspepsia is exclusively relieved by defeation or associated with the onset of a change in stool frequency or stool form (1). FD is one of the most common clinical problems in medical outpatients and is associated with considerable health and economic burden (2). The available literature reports that FD is associated with a higher lifetime prevalence of psychiatric illness, predominantly anxiety and depressive disorders (3,4). I report the efficacy of mirtazapine in treating a patient with FD and depression.

Case Report

Ms A, a 54-year-old married woman with epigastric discomfort, fullness, nausea, and postprandial bloating, was referred for what her gastroenterologist had diagnosed as FD according to Rome II criteria (5). The FD symptoms had been present episodically for the last 5 years and had been virtually unremitting for the last 6 months. The results of extensive medical evaluation, including esophageal manometry, 24-hour ambulatory intraesophageal pH monitoring, and electrogastroscopy, were negative. Her gastroenterologist had treated her with valium 2 mg 3 times daily and cisa-pride 10 mg 3 times daily, with minimal improvement.
When Ms A was seen by a psychiatrist, she met the criteria for major depression. She began treatment with mirtazapine 15 mg, which was increased to 30 mg daily after 3 days. After 4 weeks, Ms A was significantly improved and reported that mirtazapine had helped her. She stated that she had a marked decrease in all FD symptoms and an increased appetite. Her quality of life was measured with the Medical Outcomes Study 36-Item Short Form Health Survey—Korean version (SF-36-K), and depression was measured with Beck Depression Inventory (BDI).

The limbic system is involved in emotion, mood, and visceral autonomic control, and limbic abnormalities are seen in depression and functional gastrointestinal disorder (6). These indicate the relation between depression and FD. Studies of 5-HT, antagonists indicate that this pharmacologic class increases the threshold for the sensation of first perception and pain and that 5-HT subtypes mediate gastrointestinal reflexes and secretion. This blunts the visceral perception, leading to therapeutic efficacy in the inhibition of emesis and treatment of functional motility disorders (7). Because mirtazapine is an antidepressant with a postsynaptic 5-HT subblocking effect (8), it can be used to treat FD with depression.

Further study is needed of the relation between mirtazapine, depression, and the psychophysiological reaction, such as gastric emptying in FD, as indicated by electrogastrography.

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References


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Re: Using Language in Psychiatry

Dear Editor:

Fine reports that much more work re- mains to map the details of language onto the details of psychiatric disorder (1). Such mapping will eventually provide clinicians with an organized way to listen for disorders. Recent research supports this strategy: in 2 groups of men followed prospectively for 10 years (P < 0.05), an- gina or hypertension and a sixfold coro- nary incidence correlated with the rate of 1-second speech hesitation pauses (SHPs) (mean pause duration 1.5 sec- onds, SD 0.33; mean pauses/minute 4.79, SD 2.48), pauses are behavioural corre- lates of mood whose rats also correlated with immobility in the face of stress and with an increase in planning difficulty (2,3).

Neurobiological features are suggested by the correlation of rate and variability in duration of SHPs with the left and right hemisphere, respectively, by the associa- tion of reduced blood pressure with immobility in the face of stress and by the profound effects on an- gina and body-part information in the premo- tor cortex during stress is reduced by the local activation of glutamate receptors (4), by the association of 3-second inter- trial intervals with integration of target and body-part information in the premo- tor cortex when planning action (5), and by the association of 2- to 4-second peri- ods of rest with significant cognitive activity (6). These findings give precise, objective methods (2) with which to clarify the extent to which psychiatric disor- ders are related to language processing problems (1).

References


Ernest H Friedman, MD
Cleveland, Ohio

Dr Fine Replies

Dear Editor:

Dr Friedman provides data suggesting that the connection between language data and psychiatric disorders may be through a series of neurophysiological mechanisms (1). In particular, he pro- poses that the clinical observation of pausing in language is related to de- pressed mood (and perhaps to other disor- ders, such as pervasive developmental disorders) and may be controlled by a complex series of vascular and neurologi- cal events. These mechanisms must then be related to psychiatric disorders. The functional linguistic approach can be combined with precise neurobiological
measurements to provide a neurobiological account of both normal social functioning and the impairments in social functioning that are considered psychiatric disorders.

In the data presented, pauses of 2 to 3 seconds are the result of behavioural events and the speed of neurobiological processes (1). To advance our knowledge, these findings must be specifically tested on the external events relevant to different psychiatric disorders. For example, are pauses more common or longer in reaction to stressful situations—or even, at a micro level, in reaction to stressful utterances by another speaker? Pauses of 2 to 3 seconds on their own do not give maximum information. The location of the pauses in terms of language production, interaction, and hypothesized processing factors can be studied to link psychiatric disorders to underlying neurobiological mechanisms through language. In terms of language production, the location of the pauses needs to be studied at 4 stages: at the beginning of turns (when a speaker is just starting a contribution), between clauses (when the ideas may be being formulated), before content words (when word retrieval is in progress), and even within words (when articulation processes are at stake). In terms of interaction, 3 elements need to be investigated: the pauses between speakers, each speaker’s kinds of utterance (that is, statements, questions, commands, corrections, or follow-ups), and the relationship between the speakers (for example, higher social position vs subordinate social position). Finally, processing factors such as stress, information processing, planning, executive functions, and the emotional impact of topics will affect neurobiological processing, the use of language, and how that language reflects psychiatric disorders. The results will have clinical significance: they will indicate what kinds of interactions are associated with what kinds of clinically relevant linguistic productions and, specifically, pausing. They will also have significance for basic science: they will indicate what the mechanisms are behind psychiatric disorders that contribute to their language characteristics.

A sufficiently detailed functional account of language links behaviour in psychiatric disorders—what is socially dysfunctional—to the underlying neurobiological mechanisms. Neurobiological mechanisms can be related to specific characteristics of language (for example the pausing reported by Friedman [1]), and these characteristics of language can be related to the observed characteristics of psychiatric disorders. Language provides a crucial intermediate step in the analysis. It is specific enough to study neurobiologically, and it also describes the phenomena that contribute to, if not define, the social difficulties experienced by individuals with psychiatric disorders (2).

**References**


Jonathan Fine
Ramat-Gan, Israel

**Psychotic Mania in Bipolar II Depression Related to Sertraline Discontinuation**

**Dear Editor:**

Discontinuing selective serotonin reuptake inhibitors (SSRIs) may induce a syndrome wherein the main neuropsychiatric symptoms are dizziness, shock-like sensations, anxiety, irritability, agitation, and insomnia. These symptoms usually develop 1 to 7 days after either abrupt or gradual discontinuation (1–3). Antidepressant discontinuation may also induce mania, mainly reported with tricyclics and monoamine oxidase inhibitors (MAOIs) but also observed with SSRIs (4). Acute psychosis has been reported in previously nonpsychotic patients following abrupt discontinuation of the MAOI phenelzine (5). Biological mechanisms may be cholinergic overdrive activating monoaminergic systems (6) or a hyposerotonergic state arising from SSRI-induced postsynaptic serotonin receptor desensitization coupled with increased serotonin reuptake after discontinuation (7).

I report the case of a patient diagnosed with bipolar disorder II (BD II, depression and hypomania alternating) according to DSM-IV criteria. This patient had a first episode of psychotic mania soon after rapid discontinuation of sertraline. A Medline search did not find similar reports, although 2 similar cases were reported in a case series (4).

**Case Report**

A 32-year-old woman with long-term BD II had been treated during the last 2 years with sertraline 50 mg daily for depression, which had partially remitted. She was taking no other drugs, and her family doctor tried discontinuing sertraline. The patient took 25 mg daily for 1 week and then discontinued sertraline altogether. After some days, she felt anxiety, irritability, agitation, insomnia, and “electrical shocks” all over her body. A few days later, she became manic, showing marked irritability, insomnia, talkativeness, racing thoughts, psychomotor agitation, increased goal-directed activities, and marked impairment of functioning. Because she could not understand the cause of the very distressing “electrical shocks,” she became convinced that family members were inducing the shocks to kill her. The clinical picture worsened in 2 weeks, when she ran away from home for fear of being killed. At this point, she was involuntarily committed to hospital. After 2 weeks of treatment with a neuroleptic, her delusions and mania disappeared, and she became mildly depressed. In the following weeks, after the neuroleptic dosage was gradually reduced, her mood became normal.

My own long-term research on BD II supports her diagnosis. Because she had never had mania, a spontaneous cycling concurrent with sertraline discontinuation seems unlikely. However, switching from BD II to BD I during long-term follow-up has been reported in a small percentage of patients (8). Mania-related confounding elements could be antidepressant-induced mania, agitated depression, and SSRI discontinuation syndrome (4). Antidepressant-induced mania usually appears 3 to 6 weeks after...
antidepressant institution (9) and seems unlikely in this case because this patient had been taking sertraline for 2 years. Agitated depression also seems unlikely: she was agitated and manic. The timing of the symptoms suggests a link with sertraline discontinuation. However, while she showed some typical symptoms of SSRI discontinuation syndrome, psychotic mania is not listed among them (1,2). It seems that the psychotic mania presented by this patient may be related to mania induced by antidepressant discontinuation. This case presents a link between such mania and SSRI discontinuation syndrome. The link is the shock-like sensations, which she believed were induced by family members to kill her. The mechanism underlying this psychotic mania after sertraline discontinuation may be a hyposerotonergic state (7). The serotonin system is closely linked with the dopamine system: increased serotonin increases dopamine activity (10). Because increased dopamine has historically been linked to psychosis and mania (11), discontinuing sertraline may have increased dopamine activity too greatly. The bipolar vulnerability of this patient may have heightened her sensitivity to this effect. It seems likely that, owing to sertraline’s weak dopamine reuptake blockade, these biochemical effects overcame sertraline’s possible downregulating effect on dopamine receptors (12).

References


Franco Benazzi

Forli, Italy

Délirium associé à l’azithromycine

Cher redacteur :

Le délirium est rarement associé à l’administration d’antibiotiques (1). Deux cas sont ici rapportés où le délirium coïncide avec l’administration de certains antibiotiques de type macrolide au dosage quotidien de 500 mg intraveineux durant quatre jours.

Cas A

Il s’agit d’un patient de 70 ans hospitalisé depuis deux mois. Le patient a été trouvé inconscient à domicile. Il a souffert de rhodomyolise associée probablement à l’administration d’un hypolipémiant. Après un long séjour aux soins intensifs avec une ventilation mécanique de plusieurs jours, une pneumonie et un état de choc, une longue liste de complications dont une polyneuropathie et des difficultés de déglutition, le patient a demandé à être vu en psychiatrie. Il est alors alerte, grabataire. Il présente un certain cynisme lié à sa condition clinique difficile. Il n’y a pas d’élément psychotique manifeste. Le patient semble souffrir d’être complètement dépendant à cause de sa maladie. Dans les jours qui suivent, le patient fait une surinfection pulmonaire et il est traité à l’azithromycine. Au jour 1 de l’administration du médicament, aucun symptôme particulier n’est noté. Au jour 2, dès la nuit, le patient est confus, incohérent. On note des propos désorganisés et de la confusion dans le temps et l’espace. Le lendemain, le patient paraît tenir un discours délié par rapport à son frère qui aurait détruit son automobile. Il indique que le téléphone parle. On note, au jour 3, des hallucinations visuelles; le patient est confus et crie. Au jour 4, le patient est toujours confus, il parle seul, est toujours désorienté et a des hallucinations visuelles et auditives. L’administration d’antibiotiques est cessée et le patient se rétablit durant la journée qui suit en disant qu’il a eu des médicaments trop forts. Il revient alors à l’état normal antérieur tel que constaté au premier contact. Le patient ne recevait pas alors durant cette période d’autre médicament comme des narcotiques qui auraient pu être responsables de son état. Il n’y a pas eu de pic fébrile ni d’altération des ions ou enzymes hépatiques.

Cas B

C’est un patient de 75 ans qui a subi, il y a trois mois, une lobectomie supérieure droite pour une tumeur de Pancoast. Il a fait, par la suite, un long séjour aux soins intensifs pour une pneumonie avec choc septique et un syndrome de détresse respiratoire aiguë. Par la suite, durant neuf jours, il est mis sous hémofiltration et ultérieurement, une trachéotomie est pratiquée. Par la suite, une encéphalopathie est diagnostiquée. Le TDM cérébral montre un peu d’atrophie sans accident cérébrovasculaire. Le sevrage du respirateur est difficile mais est finalement accompli. Le patient est vu en consultation psychiatrique à ce moment, en récupération d’encéphalopathie. Il est vigile, présente une asthénie importante. Il est calme mais facilement dyspnée. Le contact verbal et visuel est bon quoique limité à cause de la trachéotomie. Il n’y a pas d’évidence alors de symptôme psychotique bien que le patient soit légèrement désorienté. Une semaine plus tard, le patient fait une infection respiratoire et le traitement à l’azithromycine est débuté. Peu avant le début du traitement, le
patient fait un état de détresse respiratoire et un protocole à la scopolamine 0,4 mg sous-cutané, une fois par jour, a été instauré et administré aux jours 1 et 2 du traitement à l’azithromycine. Le patient a aussi reçu de l’hydromorphone 1 mg sous-cutané 5 fois, le jour 1 du traitement et une fois le jour 2. Au jour 2 du traitement, le patient est confus, a de la difficulté à suivre du regard l’interlocuteur. Au jour 3, le patient est désorienté de façon plus importante, surtout dans l’espace. Il a des hallucinations visuelles, il voit des mouches et ses propos sont désorganisés. Au jour 4, le tableau clinique revient rapidement à la normale lorsque l’antibiotique est cessé ce jour 4. Il y a ici la possibilité de facteurs confondants par l’administration d’hydromorphone et de scopolamine. Il n’y a pas eu de pic fébrile.

Dans les deux cas, il s’agit de patients dont l’état général est dégradé et qui viennent de passer à travers une longue période de soins intensifs avec un syndrome d’immobilisation consécutif. Il y a donc possibilité de plusieurs facteurs confondants. Les paramètres des fonctions hépatiques, pancréatiques et rénales de ces deux patients sont dans les limites normales pour la période considérée. Des effets similaires ont été rapportés pour d’autres macrolides, notamment la clarithromycine (2,3). Des observations supplémentaires sont donc nécessaires pour confirmer ces deux coïncidences cliniques, assez similaires à celles rapportées avec la clarithromycine.

Sources de références


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**Behavourial Therapy for the Treatment of Alcohol Abuse and Dependence**

**Dear Editor:**

Cognitive-behavioural therapy (CBT) is a problem-focused psychotherapeutic approach based on learning theory that has been effectively used to treat alcoholism (1–3). CBT is directed primarily at modifying distorted or maladaptive conditions and altering environmental contingencies to diminish behavioural dysfunction. Dialectical behaviour therapy (DBT) is a form of CBT developed for patients with a diagnosis of borderline personality disorder (BPD) (4–6). It may be very effective as a treatment for alcohol abuse and dependence in general, as well as for patients with alcohol abuse or dependence who also meet criteria for BPD. Impulsiveness in areas that are potentially self-damaging (including substance abuse) is a criterion for BPD (7). BPD patients are frequently polydrug abusers and usually combine drug and alcohol abuse (4). A recent study has found that patients with alcoholism who relapse within 6 months of detoxification show a higher rate of personality disorders, especially BPD and antisocial personality disorder (8).

DBT is based on a biosocial theory of personality functioning: a systemic dysfunction of the emotion regulation system stems from the interactions over time of biological irregularities in conjunction with certain types of environments (4–6). DBT as a theory and therapy favours the most nonpejorative explanations for behaviour. In DBT, there are 4 behavioural targets: 1) to decrease life-threatening behaviours; 2) to decrease therapy-disrupting behaviours that may compromise treatment effectiveness (for example, arriving intoxicated for a session); 3) to decrease behaviours that interfere with quality of life (for example, alcohol abuse); and 4) to increase coping skills. The 3 modes of outpatient DBT are psychosocial groups (for skill training), individual therapy (to address motivational issues and strengthen skills), and telephone contact with the individual therapist (to address generalization). A combination of DBT and pharmacologic treatments may help some patients with alcohol abuse or dependence.

References