The search for new off-label indications for antidepressant, antianxiety, antipsychotic and anticonvulsant drugs

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2004 CCNP Heinz Lehmann Award Paper: Part I

Most drugs are prescribed for several illnesses, but it took several years for psychotropic drugs to have multiple clinical indications. Our search for serotonergic drugs in affective illnesses and related disorders led to new off-label indications for fluoxetine, sertraline, tryptophan, clonazepam, alprazolam, tomoxetine, buproprion, duloxetine, risperidone and gabapentin. Various clinical trial designs were used for these proof-of-concept studies. Novel therapeutic uses of benzodiazepines, such as in panic disorder and mania, were found with the introduction of 2 high-potency benzodiazepines, clonazepam and alprazolam, which were thought to have serotonergic properties. Our initial clinical trials of fluoxetine and sertraline led to their approved indications in the treatment of obsessive–compulsive disorder, and our trials of gabapentin led to new indications in anxiety disorders (generalized anxiety, panic attack and social phobia) and sleep disorders (insomnia).

La plupart des médicaments sont prescrits pour plusieurs maladies, mais il a fallu plusieurs années pour que les psychotropes aient de multiples indications cliniques. Notre recherche de médicaments sérotoninergiques contre des maladies affectives et des troubles connexes est à l'origine de nouveaux emplois non conformes des médicaments suivants : fluoxétine, sertraline, tryptophan, clonazépam, alprazolam, tomoxétine, buproprion, duloxétine, rispéridone et gabapentine. On a utilisé divers concepts d'essais cliniques pour ces études de validation du principe. On a trouvé de nouvelles utilisations thérapeutiques pour les benzodiazépines, comme dans des cas de trouble panique et de manie, avec l'arrivée sur le marché de deux benzodiazépines de haute puissance, le clonazépam et l'alprazolam, qui semblaient avoir des propriétés sérotoninergiques. Nos premières études cliniques sur la fluoxétine et la sertraline ont débouché sur l'approbation de leurs indications dans le traitement du trouble obsessif compulsif, et nos études sur la gabapentine sont à l'origine de nouvelles indications contre les troubles de l'anxiété (anxiété généralisée, crise de panique et phobie sociale) et du sommeil (insomnie).

Introduction

This is the first of 2 papers in which I review aspects of the research that contributed to my receiving the 2004 Heinz Lehmann award. This paper describes the clinical trials that led to new off-label indications for psychotropic drugs. The second paper describes the clinical studies carried out to define and differentiate drug-induced movement disorder (DIMD) from psychiatric symptoms.[1]

For the last 30 years, my research has focused on the role of serotonin and dopamine in the pharmacotherapy of psychiatric disorders. My interest in serotonin originated from the tryptophan research carried out by Simon Young and Ted Sourkes,[2] whereas my interest in dopamine came from its role in movement disorders induced by antipsychotic drugs. In the early 1970s, affective disorders were thought to be associated with a decrease in functional brain serotonin, whereas schizophrenia and related psychoses and movement disorders were associated with dopamine dysfunction. In affective disorders, clinical trials of tryptophan, given as a

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Medical subject headings: anticonvulsants; antidepressive agents; antipsychotic agents; anti-anxiety agents; depressive disorder, major; off-label indications; schizophrenia.

J Psychiatry Neurosci 2006;31(3):168-76.

Submitted Sept. 30, 2005; Revised Dec. 22, 2005; Accepted Jan. 10, 2006

biogenic amine precursor of brain serotonin, had been inconclusive. Young and Sourkes suggested that the uncertain effect of tryptophan as an antidepressant was related to its high rate of catabolism by tryptophan pyrrolase in the liver and recommended the use of nicotinamide to reduce its breakdown in the liver.[2] While we were investigating tryptophan given with nicotinamide to test its antidepressant effect as a biogenic amine precursor of brain serotonin,[3] we thought of drugs that could have a more direct effect on brain serotonin through their effects on serotonin receptors, thus looking at an alternative pharmacological approach to giving a biogenic amine precursor such as tryptophan or levodopa. One of these drugs was alprazolam,[4,5] an atypical benzodiazepine, and another was clonazepam,[6,7] an anticonvulsant with serotonergic effects. This was when other anticonvulsants, such as carbamazepine[8,9] and valproic acid,[10] were starting to be studied in bipolar disorder.

We then studied a third group of serotonergic drugs, the selective serotonin reuptake inhibitors (SSRIs), which act differently from the precursor, tryptophan, and not through a direct effect on the serotonin receptor as is the case for clonazepam. We started with fluoxetine given first in depression[11] and then in obsessive–compulsive disorder (OCD),[12] as well as sertraline in both depression[13] and OCD.[14] Finally, we conducted early clinical studies of a fourth group of serotonergic drugs, antipsychotics with potent serotonergic antagonist properties, first clozapine[15] and then risperidone,[16] when looking for antipsychotics to prevent DIMD through their antiserotonin effects.

New indications for psychotropic drugs

Alprazolam in panic disorder

Our search for serotonergic drugs led us to study alprazolam, an atypical benzodiazepine, in panic disorder,[4,5] a disorder treated like a major depression but officially classified as anxiety neurosis at the time. On Oct. 20, 1976, we initiated the first clinical trial of alprazolam in panic disorder, which we considered to be a serotonin disorder like depression, and found the drug to be efficacious not only for anticipatory anxiety but also to block panic attacks. Before this study of high-potency benzodiazepines, treatment of patients with panic disorder was limited to tricyclic antidepressants (TCAs)[17] and monoamine oxidase inhibitors (MAOIs), and benzodiazepines were thought to have an effect limited to anticipatory anxiety.

In this proof-of-concept study of alprazolam, we used a design that included patients who met criteria for anxiety neurosis according to the *Diagnostic and statistical manual of mental disorders*, second edition (DSM-II),[18] but who also met the Research Diagnostic Criteria (RDC) criteria[19] for generalized anxiety disorder (GAD) and/or panic disorder. At the time this study was initiated (1976), the official distinction between GAD and panic disorder was not used. In fact, it was because alprazolam was thought to have a serotonergic effect that we decided to include patients with panic disorder. Before initiating the washout period, most of the patients were treated with unselective MAOIs, which are known to increase serotonin. In this 8-week double-blind placebo-controlled study, 50 outpatients with GAD (n = 30) or panic disorder (n = 20) were randomly assigned to treatment with alprazolam or placebo. After the placebo washout period of a week, a flexible-dose drug regimen was used, and short-term behaviour therapy was conducted during the last 4 weeks. Symptoms were assessed using the Hamilton Anxiety Rating Scale (HAM-A)[20] and the Self-Rating Symptom Scale.[4,5,21]

HAM-A total scores, Somatic Anxiety scores and Psychic Anxiety scores for patients treated with alprazolam were significantly decreased compared with placebo. Anxiety and somatic complaints responded best to alprazolam treatment. Alprazolam was significantly superior to placebo for anxious mood, tension, fears, insomnia, intellectual (cognitive) functioning, depressed mood, somatic symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms and behaviour at interview. Alprazolam treatment was associated with a rapid response in patients with GAD and panic disorder, and no significant differences were found in the response to alprazolam between diagnostic groups. In addition, behaviour therapy was found to have little effect on outcome compared with alprazolam. The findings of this clinical trial were then confirmed through several multicentre clinical trials,[22–24] which led to the first official approval of a drug in the treatment of panic disorder. Shortly after, while looking for other serotonergic drugs, we found that another high-potency benzodiazepine, clonazepam, which is both a serotonin agonist and anticonvulsant, was as effective as alprazolam in the treatment of panic disorder.[7]

Clonazepam in mania

After our clinical trial of alprazolam in panic disorder, while pursuing the search for serotonergic drugs, we initiated, in collaboration with Young and Annable,[6] the first study of clonazepam in psychiatric patients on Oct. 28, 1979. At that time, we had 2 hypotheses for the use of clonazepam. The first hypothesis was that clonazepam had anticonvulsant properties,[25] especially for seizure disorders where serotonin might be involved and, second, that clonazepam had a serotonin agonist effect.[25,26] Both properties were thought to be associated with antimanic effect,[6] because other anticonvulsants were also starting to be given for bipolar illness and because mania was associated with central serotonin dysfunction. Because of the known sedative effect of clonazepam, we decided to initiate this proof-of-concept study of clonazepam with a different study design from that used for our alprazolam study. We studied the antimanic effects of clonazepam in a double-blind crossover design with 9 men and 3 women who had been newly admitted to hospital from the emergency department for acute mania. The treatments compared were 10 days of clonazepam therapy at doses of 2–16 mg/d and 10 days of lithium therapy at doses of 900–2100 mg/d. The results showed that clonazepam was significantly more efficacious than lithium on the "motor activity" and "insight" mania items on the Inpatient Multidimensional Psychiatric

Scale.[27] Clonazepam was also shown to be significantly safer with regard to motor side effects, including parkinsonism.

We concluded that clonazepam was highly sedative and well tolerated at high doses in treating patients with acute mania. Clonazepam was more efficacious than lithium in reducing acute manic symptoms but, more important, as-needed doses of haloperidol were fewer and the number of days on which it was needed was lower during clonazepam treatment. By reducing the need for antipsychotic drugs in the treatment of acute mania, clonazepam reduces the risk of side effects in these patients.[28] Shortly after, lorazepam, another high-potency benzodiazepine with anticonvulsant properties, was found to be efficacious as adjunctive treatment in mania and agitation.[29,30] Later, the combined use of a benzodiazepine and the antipsychotic haloperidol was established as the most efficacious treatment of acute agitation in the emergency department.[31–38]

Clonazepam in panic disorder

Because panic disorder was associated with a serotonin disturbance, we initiated the first clinical trial of clonazepam in panic disorder[7,39] owing to its serotonergic properties. We used an open-label design that was different from the double-blind design used in our 2 previous proof-of-concept studies.[4,6] Our results were confirmed later in several double-blind placebo-controlled studies[40–42] and led to approval by the US Food and Drug Administration (FDA) of clonazepam as an antipanic agent on Dec. 23, 1997.

In this first study carried out in 1983, we treated 12 patients diagnosed with panic disorder according to the *Diagnostic and statistical manual of mental disorders*, third edition (DSM-III), criteria.[7,39,43] Ten patients showed marked improvement in the severity of their anxiety symptoms as measured by the HAM-A[20] and the Hopkins Symptom Check List (HSCL-90).[44] These results suggested that clonazepam was as effective as alprazolam in the treatment of panic and, in addition, had the advantage of leading to less rebound anxiety upon cessation because of its longer half-life.

Later, we followed 8 patients, of whom 7 were diagnosed with agoraphobia with panic attacks and 1 with panic disorder, and all of whom were treated with clonazepam over a 7-week to 16-week period.[45] Of these 8 patients, 5 had been unsuccessfully treated with diazepam, lorazepam or amitriptyline or another pharmacological agent. Patients were assessed with the HSCL-90, and all showed significantly decreased mean scores for the anxiety dimension, phobic anxiety dimension and the panic attack symptoms. Phobic avoidance, anticipatory anxiety and free-floating anxiety also significantly improved in all patients. These results prompted the start of double-blind placebo-controlled trials.

The use of clonazepam in the treatment of panic disorder was later confirmed by one of our double-blind placebo-controlled trials, where we found a significant correlation between clonazepam plasma concentrations and Clinical Global Impression of Severity (CGI-S)[21] panic disorder scores.[46] CGI-S panic disorder scores significantly decreased with the administration of clonazepam compared with placebo during a period of 4 weeks. Numerous randomized placebo-controlled trials[23,24,41,42] confirmed our initial results and showed that the high-potency benzodiazepines, such as alprazolam and clonazepam, are efficacious in the short-term treatment of panic disorder. These trials led to FDA approval of both alprazolam and clonazepam in panic disorder. Furthermore, benzodiazepines were shown to be efficacious in the long-term management of panic disorder at low doses.[47,48]

Rebound anxiety, supersensitivity psychosis and new indications for benzodiazepines

As investigation of benzodiazepines continued, new concepts emerged in benzodiazepine therapy, such as classification of the effects of benzodiazepine withdrawal and new indications for the more potent benzodiazepines. In 1986, we proposed a new classification of phenomena associated with drug discontinuation and differentiated between relapse, withdrawal syndrome, supersensitivity psychosis and rebound anxiety.[49] We defined a relapse as a return of the original disorder, whereas a withdrawal syndrome is the appearance of new symptoms, which can be divided into major and minor withdrawal symptoms, according to their severity.[7,50] Rebound anxiety is a temporary return of symptoms present at a greater intensity than in the original illness. The phenomenon of rebound anxiety became more prevalent as benzodiazepines with short half-lives were introduced and made withdrawing medication more difficult. In 4 of our placebo-controlled studies with anxious patients who met DSM-III criteria, we investigated this phenomenon by looking at the effects of withdrawing benzodiazepines that had different half-lives.[51] We defined rebound anxiety as an increase of 10% or more above untreated baseline levels in total scores for both HAM-A[20] and the Self-Rating Symptom Scale.[21] We found that the prevalence of rebound anxiety with benzodiazepines was higher with abrupt medication withdrawal and, in addition, with benzodiazepines that have short-to-intermediate half-lives and no potentially active metabolites.[50] The length of earlier treatment with benzodiazepines had no effect on the appearance of rebound anxiety.

We also described another withdrawal syndrome that we labelled supersensitivity psychosis,[52–54] which manifests itself after the long-term use of neuroleptics and antipsychotics. After decrease or discontinuation of a neuroleptic, there can be a sudden relapse with both new and rebound symptoms associated with supersensitivity of dopamine receptors, potentially accompanied by a development of central nervous system tolerance to the antipsychotic effect of neuroleptics. The re-establishment of the neuroleptic dosage shows a rapid improvement in supersensitivity psychosis. Although the rebound phenomena are similar to symptoms seen with this supersensitivity phenomenon, they have different pharmacological mechanisms and outcomes.

Benzodiazepines were classified by low, medium and high potency, because different therapeutic indications required benzodiazepines of different potencies.[51] High-potency benzodiazepines, such as alprazolam, clonazepam and bromazepam, were associated with a greater anxiolytic effect

than the classic benzodiazepines. As discussed above, new psychiatric indications for these high-potency benzodiazepines were discovered for the treatment of panic disorder and mania. The advancement in anxiety disorder conceptualization and treatment coincided with the new DSM-III classification in the early 1980s of anxiety disorders into 3 main categories: GAD, panic disorder and OCD.

Lithium–tryptophan in affective disorders

The involvement of serotonin in affective disorders led us to investigate tryptophan, a biogenic amine precursor of serotonin, and the lithium–tryptophan combination. We conducted 7 clinical trials of the use of tryptophan in affective illness, first as an antidepressant,[55–57] an antimanic[57,58] and, finally, as a mood stabilizer[58,59] when administered in combination with lithium. We completed a randomized crossover 1-year study in treatment-resistant patients (n = 100) using the lithium–tryptophan combination,[60] which led to the approval in Canada of a unique indication for tryptophan as an adjunctive medication to lithium. Unfortunately, the drug was withdrawn from the US market following reports of eosinophilia–myalgia syndrome occurring in the United States.[61,62] However, no cases of eosinophilia–myalgia, or even significant increases in eosinophilia count, were found during all our clinical trials with tryptophan[4,55–60] in Canada (unpublished observations).

Tomoxetine in major depression and attention-deficit hyperactivity disorder

On Mar. 1, 1983, we undertook the first proof-of-concept study of tomoxetine in major depression, because it was a selective inhibitor of the uptake of noradrenaline with little affinity for adrenergic receptors.[63] This 12-week open-label study included 10 newly admitted depressed patients diagnosed with recurrent unipolar major depressive disorder according to DSM-III criteria, who all had a score of at least 20 on the Hamilton Rating Scale for depression (HAM-D).[64] After a 1-week placebo washout period, patients received tomoxetine for an initial 6 weeks and then for an additional 6 weeks for follow-up.[65] An initial dose of 40 mg/d was increased if necessary by 10-mg/d increments at a minimum interval of 3 days to a maximum of 70 mg/d. The results showed a significant reduction in mean total HAM-D scores, as well as significant improvement on the CGI-S. In addition to the antidepressant effect of tomoxetine, we observed that all patients complained at one time of sleeping difficulty during treatment. We hypothesized that the potentiating effect of tomoxetine on noradrenergic function could explain the side effects reported such as insomnia, agitation or hyperactivity, and palpitations or feelings of increased heart rate. Later, the group at Massachusetts General Hospital, Boston, was the first to report the beneficial effects of tomoxetine in the treatment of attention-deficit hyperactivity disorder (ADHD) in a double-blind, placebo-controlled, crossover study with adult patients (n = 22).[66] Tomoxetine was found to be effective in the treatment of ADHD and was well tolerated at an average dose of 76 mg/d. The average improvement rate of ADHD symptoms with tomoxetine was similar to that obtained in trials with methylphenidate, and atomoxetine was later approved by the FDA in 2002 as the first nonstimulant for the treatment of ADHD.

Duloxetine in major depression and neuropathic pain

After the second generation of antidepressants, including the SSRIs and bupropion, the selective serotonin–noradrenaline reuptake inhibitors (SNRIs) emerged as a new class of effective antidepressants.[67] Duloxetine is an SNRI and inhibits the reuptake of noradrenaline, serotonin and dopamine, although it is a 3- to 4-fold more potent inhibitor of serotonin. We initiated a proof-of-concept study using a multicentre double-blind placebo-controlled and active comparator–controlled trial (n = 600, total; n = 44, Allan Memorial Institute; n = 150, Canada) of duloxetine in outpatients with major depression and included our first patient on Jan. 14, 1994. We used an original drug design with 3 phases, an acute therapy phase, an extension phase for responders and a de-escalation phase for 2 weeks. After a 1-week placebo washout period, patients were randomly assigned to placebo, clomipramine, which was the control drug, or 1 of 3 fixed doses of duloxetine (5 mg, 10 mg or 20 mg) for 8 weeks. Patients whose condition improved from baseline were allowed to continue in the double-blind extension phase of 44 weeks' duration. Unfortunately, the investigation of the drug was interrupted and restarted at a later time. Duloxetine was shown to be efficacious in the treatment of depression.[67] Interestingly, later studies showed that duloxetine was efficacious for the treatment of neuropathic pain associated with diabetic peripheral neuropathy,[68] and its use in neuropathic pain was approved by the FDA in 2005.

Bupropion in depression and smoking cessation

Proof-of-concept studies of bupropion were carried out in 2 multicentre trials comparing bupropion and amitriptyline in depressed patients[69] and showed bupropion to be efficacious in the treatment of depression. This proof-of-concept study remains of interest, because the mechanism of action of bupropion as an antidepressant remains largely unknown and because it differs from standard antidepressants in that it has little effect on noradrenaline or serotonin reuptake and does not block muscarinic, histaminic or α-adrenergic receptors. However, it inhibits the neuronal reuptake of dopamine to some extent.[69] In addition, we found that it did not induce orthostatic hypotension as TCAs did.[70] In the first multicentre study, we included 124 outpatients with depression who were randomly assigned to receive bupropion or amitriptyline for 13 weeks, preceded by a 1-week washout period and followed by a 1-week withdrawal period. Patients were included if they met the FDA Guidelines for the Clinical Evaluation of Antidepressant Drugs[71] and had a total score on the HAM-D of at least 18 at screening. Bupropion was given on an equally divided (3 times a day) regimen, first at 300 mg/d, and then the dose was increased to 450 mg/d during the second week.

In the second study, we included 92 inpatients with depression, using the same criteria, and compared bupropion and amitriptyline treatment for a 6-week period. The dosage of bupropion was also increased from 300 mg/d to 450 mg/d and then further increased to a maximum of 750 mg/d.

Initial results from both these studies showed that bupropion was as effective as amitriptyline in the treatment of depression. Both treatment groups had more than 50% improvement on HAM-D total scores, and improvement was also seen on the CGI-S. Bupropion did have a slightly lower overall therapeutic effect during the first 4 weeks of treatment; however, it was not significant. There were mild dopaminergic side effects in patients treated with bupropion, but amitriptyline induced more weight gain and had more anticholinergic, antihistaminic and antiadrenergic side effects. These results supported the use of bupropion as an antidepressant. It is worth noting that we used a similar drug design as in our proof-of-concept study of fluoxetine in depression. Later, bupropion was found to have another indication and was approved by the FDA in May 1997 for smoking cessation.[72] Bupropion is unique as a smoking cessation drug, because it does not contain nicotine.

Zimeldine in OCD and no crossover hypersensitivity reactions with other SSRIs

Serotonin was also thought to be implicated in the pathophysiology of OCD.[73] Patients with OCD who were treated with clomipramine[74–77] showed more improvement than patients treated with other antidepressants. In contrast to other antidepressants, clomipramine was a more potent serotonin reuptake inhibitor, although not selective. With the introduction of the new selective SSRIs, Kahn and collaborators conducted the first clinical trial of zimeldine in the treatment of OCD.[78]

In order to further investigate the role of serotonin in OCD, we conducted a 6-week proof-of-concept study of zimeldine.[79] The patients (n = 9) who were treated with zimeldine met OCD criteria according to DSM-III and had a score on a modified HAM-A of at least 35 (each item rated on 7-point scale instead of 5-point scale). In addition, the patients had all been treated with antianxiety and/or antidepressant drugs for at least 1 week before the beginning of the study, and the duration of their present episode of OCD was 3–276 months. Two patients could not be included because of withdrawal of the drug from clinical investigation. After a 1-week placebo washout period, the dose of zimeldine given was started at 100 mg/d and increased to a maximum of 500 mg/d. The results showed a significant reduction in the mean total score for the obsessive–compulsive subscale of the Comprehensive Psychopathological Rating Scale (CPRS-OC).[80] Significant improvement was also seen on the CGI-S and the HAM-A scales. These results supported the use of the new class of serotonergic antidepressants in the treatment of OCD.

Zimeldine was removed from use as an antidepressant due to hypersensitivity reactions, which could be followed by Guillain–Barré syndrome.[81,82] In 1984, we reported a case of a patient with depression who developed a hypersensitivity reaction to zimeldine with joint pain, chills and headache.[83] One week after discontinuation of zimeldine, she was treated with fluoxetine and continued treatment for 4 months without any hypersensitivity reactions. This case report was important in the further development of SSRIs, because it showed that there was no crossover of the hypersensitivity reaction between fluoxetine and zimeldine. This established that the mechanism giving rise to the reaction was specific to zimeldine and, therefore, could not be the common mechanism of the SSRIs of serotonergic reuptake blocking.[83]

Fluoxetine in major depression and OCD

Pursuing our search for serotonergic drugs and looking at the third group of drugs that act through inhibition of reuptake of serotonin, on Feb. 11, 1981, we initiated the first proof-of-concept study of the new SSRI, fluoxetine, in the treatment of major depression.[11] Fifty-one patients were randomly assigned to receive fluoxetine or amitriptyline for 5 weeks. The patients included in the study met the RDC criteria for major depressive disorder, had a HAM-D score of at least 20 and had a Raskin Depression Scale score[21] that exceeded the Covi Anxiety Scale score.[21] After a 1-week placebo washout period, the dosage of fluoxetine was started at 20 mg/d and then increased to 40 mg and subsequently to 80 mg if well tolerated. Patients were evaluated with HAM-D, Raskin and Covi scales and CGI–S, and the results obtained with fluoxetine were comparable with those obtained with amitriptyline. Furthermore, patients treated with fluoxetine had a significantly better Efficacy Index–Side Effects rating[21] and also had fewer anticholinergic autonomic side effects than experienced by amitriptyline-treated patients. Later, we carried out several studies of the drug, and we initiated the final study that led to its approval as an antidepressant by the FDA in 1988 after ruling out its potential to cause phospholipidosis in humans.[84]

Following our clinical trial with zimeldine,[79] in order to further investigate the involvement of serotonin in OCD, we decided to examine the effects of fluoxetine. In 1983, we initiated the first proof-of-concept study of fluoxetine in the treatment of patients diagnosed with OCD according to DSM-III criteria.[12,85,86] This was a 9-week open-label study with 7 patients who received 8 weeks of fluoxetine treatment after a 1-week placebo washout period. All the patients had been treated before this study with antidepressant and/or antianxiety drugs for at least 1 week, and their treatments had provided some relief of symptoms but were considered unsatisfactory. To be included in this study, patients had to have a score of at least 10 on the CPRS-OC.[80] None of the patients included had diagnoses of dysthymic disorder. An initial dose of 40 mg/d was given, and the dose was increased to 60 mg on day 4 and then to 80 mg on day 7. Improvement was seen in 5 of the 7 patients, with significant reduction in the mean total score on the CPRS-OC and significant improvement on the total scores of the CGI-S, HAM-D[64] and HAM-A.[20]

These results were similar to those that had been found with clomipramine and zimeldine. However, 6 of the 7 patients had been treated with clomipramine before entering the fluoxetine study, and all had experienced significant

adverse effects that interfered with their daily lives, in contrast to the better tolerability seen with fluoxetine. Zimeldine had previously had the same beneficial effect as fluoxetine on 5 of these patients and also without the impairing adverse effects seen with clomipramine. Fluoxetine had the same efficacy as clomipramine, but with few adverse effects because it has little effect on the noradrenergic system. We concluded that as fluoxetine has a greater specificity, it was preferable to use it in the treatment of OCD compared with clomipramine. Interestingly, the use of fluoxetine was also associated with fewer withdrawal symptoms on cessation than other SSRIs used at that time.

Later, we undertook a long-term study of fluoxetine in the maintenance treatment of OCD in 50 patients with treatment-resistant OCD.[87] These patients had a diagnosis of OCD according to DSM-III, a score of at least 8 on the CPRS-OC[80] and showed resistance to conventional therapies or could not tolerate clomipramine, TCAs or MAOIs. Fluoxetine was given at a mean dose of 78 mg/d for at least 12 months. After this 1-year treatment period, 43 patients (86%) had responded to the fluoxetine treatment, as was seen by a decrease in the CPRS-OC score and CGI-S. Thirty-five patients who responded well during the treatment phase were then followed for at least an additional 12 months after discontinuation of fluoxetine. Only 8 of these patients relapsed after discontinuation of fluoxetine, a rate of relapse lower than that seen with patients treated with clomipramine in our clinics. The results of this study showed a persistent antiobsessive effect of fluoxetine and led to further investigation of the drug in OCD and its later approval as an antiobsessive agent.

Sertraline in OCD

Another drug from the third, SSRI group of serotonergic drugs, sertraline, was investigated in an early double-blind placebo-controlled trial of sertraline in major depression.[13] During this clinical trial, we reported a case of hypomania induced by sertraline.[88] Because we had evidence that the 2 SSRIs fluoxetine and zimeldine had beneficial effects in OCD, very likely through their serotonin reuptake inhibition, we initiated the first proof-of-concept study of sertraline in OCD, using a double-blind multicentre clinical approach.[14]

This double-blind placebo-controlled study with 6 different study sites included 87 patients with a DSM-III diagnosis of OCD, without depression.[14] Patients were randomly assigned to sertraline or placebo after a 1-week washout period. Treatment was followed for 8 weeks, with the first 2 weeks being a titration period during which the once-daily dose of sertraline was adjusted from 50 mg/d to a maximum dose of 200 mg/d. The adjusted dose was maintained until the eighth week, and sertraline was then tapered off over a period of 2 weeks. Patients were evaluated at baseline by the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS),[89] the US National Institute of Mental Health (NIMH) General Obsessive–Compulsive Scale,[90] the Maudsley Obsessive–Compulsive (MOC) Inventory[91] and CGI-S. The results showed that sertraline had a significantly superior effect on OCD symptoms than placebo. The Y-BOCS total score, NIMH scores and CGI-S were significantly superior for patients treated with sertraline.

In a second study, we examined the efficacy of 3 dose levels of sertraline compared with placebo in the treatment of nondepressed adult outpatients with OCD.[92,93] Patients from 11 sites (n = 325) were followed over a 1-year treatment period after 1 week of single-blind placebo washout. Patients were randomly assigned to 12 weeks of double-blind treatment with 50-mg, 100-mg or 200-mg fixed doses of sertraline or placebo. Patients who responded to treatment were offered 40 more weeks of double-blind treatment, continuing the same dose. The efficacy of the treatments was evaluated by the Y-BOCS,[89] the NIMH Global Obsessive–Compulsive Scale,[90] CGI-S and the MOC Inventory.[91] Significantly greater improvement was seen with patients in the sertraline group compared with placebo-treated patients on all measures. A significant effect was also found at end point for all 3 investigator-rated scales with the 50-mg and 200-mg doses of sertraline. These results confirmed our hypothesis of sertraline's beneficial effects and its safety in the long-term treatment of patients with OCD. SSRIs showed a slightly greater efficacy than other antidepressants and between them had similar efficacies, similar to that of clomipramine.[93] The effect of the SSRIs in OCD can be explained by a specific inhibition of serotonin reuptake. The FDA approved sertraline for the treatment of OCD on Dec. 7, 1999.

Risperidone in Tourette's syndrome

The fourth class of serotonergic drugs that we investigated were the antipsychotic drugs with antiserotonin properties,[15,16] which we hypothesized could prevent DIMD, including Tourette's abnormal movements. Following open-label studies of risperidone in the treatment of Tourette's syndrome (TS),[94,95] we further investigated the efficacy and tolerability of risperidone in the treatment of TS by conducting the first double-blind placebo-controlled, dose-ranging clinical trial.[96] Forty-eight adolescent and adult patients with TS according to the *Diagnostic and statistical manual of mental disorders*, third edition, revised (DSM-III-R)[97] criteria, and with a Global Severity Rating score on the TS Severity Scale (TSSS) of at least 3, were included in the study starting in October 1993. Patients were randomly assigned to doses of 0.5–6.0 mg/d of risperidone or to placebo for 8 weeks. During the first week of treatment, patients were assigned to fixed doses in increasing increments and afterwards were assigned to flexible dose regimens based on clinical response. The results showed that at a median dose of 2.5 mg/d, risperidone was significantly superior to placebo on the TSSS. We found that 60.8% of patients with risperidone showed an improvement of at least 1 point on this 7-point scale compared with the 26.1% of the placebo group who showed improvement. There was also improvement of global functioning in patients treated with risperidone who had average to above-average impairment at baseline on the Global Assessment of Functioning scale.[97] These results confirmed the findings of the initial studies by showing the beneficial effect of risperidone in the treatment of TS. Furthermore, patients treated with risperidone had mild and

infrequent extrapyramidal symptoms. Using the Extrapyramidal Symptom Rating Scale (ESRS),[98] no significant differences were found between the placebo group and the risperidone group for dystonic reactions, dyskinetic movements, subjective parkinsonism or akathisia. Hypokinesia and tremor did increase in the risperidone group; however, the increase in tremor was found in subjects with higher baseline tremor scores. The efficacy of risperidone in the treatment of TS was later supported by additional double-blind studies.[99–101]

Gabapentin in anxiety and insomnia disorders

Finally, the last proof-of-concept study that will be presented in this article concerns the antiepileptic drug gabapentin, for which the mechanism of action has not been completely elucidated. In August 1994, we initiated the first clinical trial of gabapentin in psychiatric disorders.[102] In the mid-1990s, gabapentin was a new oral antiepileptic drug, an analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). We decided to investigate its long-term beneficial effects in patients who needed adjunctive anticonvulsant therapy and/or benzodiazepines and who had a primary or comorbid anxiety disorder. We included 18 patients, 15 of whom were treated with gabapentin for at least 12 months. Ten patients were diagnosed with schizophrenia, 4 with schizoaffective disorder, 3 with bipolar illness (of these 17 patients, 4 had comorbid panic disorder, 4 had comorbid alcohol dependency, 2 had comorbid obsessive–compulsiveness, 1 had comorbid generalized anxiety and 1 had drug dependency) and 1 patient had generalized anxiety with comorbid major depression. These patients all required concomitant psychiatric medications such as lithium, antidepressants, antipsychotics or other anticonvulsants. The administered dosage of gabapentin varied between 200 mg/d and 1800 mg/d. When they started their treatment with gabapentin, most patients had their current anticonvulsant drug, valproic acid, discontinued. We observed an improvement in 14 of the patients regarding somatic complaints, panic, obsessive–compulsive symptoms, psychotic anxiety, generalized anxiety and insomnia, and these effects were long lasting. All the patients had improved sleep and reduced anxiety. We concluded that when given adjunctively with lithium, antipsychotics, antidepressants or other anticonvulsants, gabapentin reduced anxiety, panic attacks and insomnia and was an efficient substitute for valproic acid and benzodiazepines for long-term therapy. Benzodiazepines are thought to act through their own benzodiazepine receptor, coupled with the GABA receptor, and we proposed that gabapentin does the same through its own receptor, also coupled with the GABA receptor. Gabapentin was also reported to be efficacious as adjunctive therapy in patients with a variety of psychiatric disorders.[103–105]

Through its unique mechanism of action as an anticonvulsant, gabapentin was also found in double-blind placebo-controlled clinical trials to be effective in treating panic[106] and social phobia.[107] We proposed a multicentre study examining the efficacy and safety of gabapentin in panic disorder.[106] This was an 8-week double-blind placebo-controlled study with 103 patients diagnosed with panic disorder, with or without agoraphobia, according to the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV), criteria.[108] They also were required to have had at least 1 panic attack per week for the 3 weeks preceding the screening. After a 1-week placebo washout period, patients were randomly assigned to 600–3600 mg/d of gabapentin or to placebo. The dosage was flexible and increased if symptoms were still present, and if adverse effects were not limiting. After 8 weeks, the treatment was tapered off for 1 week. Patients were evaluated with the Panic and Agoraphobia scale (PAS). No significant differences were found between the placebo group and the group receiving gabapentin. However, as the baseline PAS scores were lower in this study than those usually reported in the literature, patients were stratified into 2 groups, one of which included patients with PAS scores lower than 20 and the other, patients with PAS scores of 20 or more. In the group with PAS scores of 20 or more, a significant decrease in PAS total scores was found in patients treated with gabapentin compared with patients treated with placebo. This study also found that women in this group showed a greater response than men whether they were treated with gabapentin or placebo. This study showed a relation between baseline severity of illness and drug response, because the evaluation of severely ill patients, with PAS scores of 20 or more at baseline, showed the greatest improvement. The interest in gabapentin is further due to its good tolerability and also to its lack of drug-to-drug interactions, because it does not undergo liver metabolism.

Gabapentin was found to have other therapeutic uses in the treatment of neuropathic pain, such as postherpetic neuralgia[109] and painful diabetic neuropathy,[110] and in the treatment of migraine.[111] Recently, a derivative of gabapentin, pregabalin, was also found to be efficacious in the treatment of neuropathic pain associated with diabetic neuropathic pain and postherpetic neuralgia[112] and was approved by the FDA in 2005.

Conclusion

In conclusion, our proof-of-concept studies for fluoxetine, sertraline, tryptophan, clonazepam, alprazolam, tomoxetine, buproprion, duloxetine, risperidone and gabapentin led to new off-label psychiatric indications. This review also illustrates how psychotropic drugs could have other medical indications approved as new clinical effects are discovered.

Competing interests: Dr. Chouinard has acted as a consultant for Solvay, Organon, Pfizer, Schering-Plough and Neuro3d.

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