Pregabalin May Cause Dependence Even if It Is Not Abused

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Abstract

Introduction and Aims: Pregabalin is approved in Norway for the treatment of epilepsy, peripheral and central neuropathic pain and anxiety. Increasing use has led to concern among professionals about the abuse potential of the drug. Some attempts have been made to explore the abuse and addiction potential of pregabalin, but these has not been conclusive. The aim of our study was to investigate this further.

Design and Methods: We interviewed six psychiatric patients at an outpatient clinic for a case series. The Norwegian version of M.I.N.I International Neuropsychiatric Interview was used to diagnose pregabalin abuse or dependence, yielding a DSM-IV diagnosis.

Results: Five of the six subjects fulfilled DSM-IV criteria for pregabalin dependence. All five of these patients had co-morbid psychiatric conditions. Two subjects were still dependent on pregabalin at the time of the interview. Both of these had a history of alcohol or other substance abuse. Two subjects met DSM-IV criteria for abuse previously, but not currently.

Discussion and Conclusions: Patients with chronic disease are more or less "dependent" on their medication. These patients may have problems with withdrawal which might falsely be labeled as addiction. The cases presented here suggest that the use of pregabalin may lead to drug dependence without abuse.

Keywords: Pregabalin; Psychiatry; Dependence; Abuse

Introduction

Pregabalin is a structural analogue of GABA. Despite the similarities, pregabalin does not act as a ligand for the GABA_A receptor-complex. The drug is ligand for the δ subunit of presynaptic voltage-gated Ca^{2+} channels. This inhibits the influx of Ca^{2+} ions into the presynaptic membrane and prevents the release of excitatory neurotransmitters such as glutamate, noradrenaline and substance P and thereby causes a decrease in central neuronal excitability [1].

There are growing concerns about abuse of prescription drugs [2,3], including pregabalin. Pregabalin was originally marketed as an anticonvulsant, but in 2004 it was also approved in Norway for the treatment of peripheral neuropathic pain. In 2006, the application was extended to include anxiety and central neuropathic pain. The increasing use of the drug has led to concern among professionals about its abuse potential[4]. Pregabalin was put on the schedule V list in America in 2005 [5] and on the list of pharmaceutical drugs under special surveillance in Norway in January 2010[6].

There have been some attempts to explore the addiction and abuse potential of pregabalin. Animal studies show that, unlike many addictive drugs, it has no effect on the reward center in the brain [7]. In a large clinical controlled study, 4% of pregabalin users experienced euphoria [8] whereas only 1% of the control group experienced this. The researchers behind this study concluded that the euphoria could be an adverse effect of pregabalin, but did not speculate further on its potential for abuse and dependence.

In 2010, the American Journal of Psychiatry published the first case report on a patient who had abused pregabalin [9]. With the explicit intention of experiencing euphoria, the patient initially started with a small dose but increased it gradually because of tolerance to the euphoric effect. On admission to hospital, he had taken 25 capsules or 7500mg of pregabalin daily (the therapeutic dose is 150-600 mg/day). This particular case also fulfilled all the DSM-IV criteria for dependence.

A Swedish pharmacoepidemiological study used data from the Swedish national register of adverse reactions. This study concluded that pregabalin is very likely to have abuse potential [10]. Several other studies have raised concern about the abuse potential of pregabalin [11-13].

These findings corresponded well with our clinical experience so we wanted to explore the potential for abuse and dependence of pregabalin further by investigating a series of patients thought to have problems with the drug.

Material and methods

Study group

We interviewed six psychiatric patients at an outpatient clinic in a small city in Norway. This city was chosen because of the relatively high use of pregabalin. This county has 5.27 users of pregabalin per 1000 inhabitants compared to a Norwegian average of 3.41. Two male and four female patients were recruited through a psychiatrist at this outpatient clinic. The inclusion criterion was pregabalin use for at least one month. The patients received written and verbal information about the project. Informed consent was obtained from the patients. Each interview was carried out over two sessions, lasting approximately 3 hours in total.

Instruments

The Norwegian version of M.I.N.I International Neuropsychiatric Interview (MINI) was used to diagnose pregabalin dependence or a DSM-IV diagnosis of abuse. MINI covers 17 axis I categories and has good correlation with the Structured Clinical Interview for DSM Disorders-I (SCID-1) and the Composite International Diagnostic Interview. MINI has also shown good psychometric properties [14,15]. MINI contains multiple modules. We used only the drug dependence and abuse questions and added some open-ended questions. If the patient met three or more of seven criteria in the dependence module, he or she was considered to be "pregabalin dependent" (Table 1). In the module designed to diagnose abuse, meeting one of four criteria was sufficient to be diagnosed with pregabalin abuse. MINI guidance is that drug abuse should not be diagnosed if addiction is present because dependence...
takes precedence over abuse. But, we asked the abuse questions in addition to see whether there was ongoing abuse or if abuse had been a part of dependence development. Other psychiatric diagnoses were taken from patient records or more unstructured patient-history taking.

**Results**

A short list of findings from patients is presented in table 2.

### Table 2: Findings from the interviewed users of pregabalin.

<table>
<thead>
<tr>
<th>Case 1 Ms.A</th>
<th>Case 2 Mrs.B</th>
<th>Case 3 Mr.C</th>
<th>Case 4 Mrs.D</th>
<th>Case 5 Mr.E</th>
<th>Case 6 Ms.F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td>29</td>
<td>50</td>
<td>50</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Current pregabalin use?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Highest single dose ever (mg)</td>
<td>600</td>
<td>900</td>
<td>1200</td>
<td>300</td>
<td>1200</td>
</tr>
<tr>
<td>Highest dose over time (mg/day)</td>
<td>900</td>
<td>900</td>
<td>1500</td>
<td>300</td>
<td>1200</td>
</tr>
<tr>
<td>Current dose pregabalin (mg/day)</td>
<td>600</td>
<td>300</td>
<td>-</td>
<td>75</td>
<td>1200</td>
</tr>
<tr>
<td>Duration of pregabalin use (months)</td>
<td>16</td>
<td>54</td>
<td>8</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Other psychotropic drugs</td>
<td>Quetiapine</td>
<td>Quetiapine</td>
<td>Quetiapine, Lamotrigine, Lithium</td>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td>Tried stopping pregabalin?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Succeeded stopping pregabalin?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>None</td>
<td>Weight gaining, Memory loss, Somnolence</td>
<td>Memory loss</td>
<td>None</td>
<td>Tremor, Weight gain and involuntary movement</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>GAD, PTSD, Anorexia nervosa, Emotionally unstable personality disorder</td>
<td>GAD, Personality disorder, Bipolar disorder II, GAD</td>
<td>GAD, Bipolar disorder, Major depressive disorder</td>
<td>Anxiety</td>
<td>GAD</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Essential hypertension, Chronic fatigue syndrome, Whiplash associated disorder</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>DSM-IV pregabalin dependence. Number of criteria met*</td>
<td>6</td>
<td>0(5)</td>
<td>0(4)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>DSM-IV pregabalin abuse. Number of criteria met*</td>
<td>None</td>
<td>0(1)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other substance abuse?</td>
<td>Multiple</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Alkohol</td>
</tr>
<tr>
<td>Other abuse still going on?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Number in bracket is number of criteria fulfilled in the past (not last 12 months but before that); N/A = Patient could not recall exact dose.

**Case 1 (29-year female, Ms A)**

Ms. A had an unstable childhood with sexual abuse and violence from an early age and a suicide attempt at the age of 13, but also more stable periods. She moved to Norway and married at the age of 18. She had regular contact with a psychologist from the age of 20. The psychologist gave her Fluoxetine for her anorexia nervosa, Oxazepam and Zopiclone for her anxiety and insomnia.
From the age of 23 she stopped working, started seeing a psychiatrist and was given Cognitive Behavioral Therapy (CBT) and Quetiapine against delusions. At the age of 24, she was diagnosed with Post-Traumatic Stress Disorder (PTSD), emotionally unstable personality disorder and Generalized Anxiety Disorder (GAD). For her GAD, she was prescribed pregabalin starting at 75mg/day. During a lengthy stay in a health institution, she was sexually abused, worsening her problems. She started cutting herself and struggled with flashbacks, feelings of shame, panic attacks and anxiety. During this period, she abused substances like heroin, morphine, marijuana, diazepam and others.

At interview, DSM-IV questions for diagnosing pregabalin abuse were negative. The patient had used pregabalin mainly for her GAD and not to induce euphoria. The patient's biggest concern was that she would not have a “normal” life without pregabalin. She was worried about her dependence on pregabalin.

Six of seven DSM-IV criteria for dependence on pregabalin were positive. The patient developed tolerance for pregabalin, which led to difficulties stopping use. She had tried twice to stop using the drug, but had failed, mostly because of withdrawal symptoms such as depression, tiredness, restlessness, irritability and tremors. She frequently used higher doses than prescribed. She spent a great deal of time obtaining and using pregabalin. She continued to use pregabalin, despite knowing she had physical problems that were likely to have been caused by the substance. She did not give up or reduce her social, occupational or recreational activities because of pregabalin. Rather, she could endure more activities because of pregabalin.

**Case 2 (50-year female, Mrs. B)**

Mrs. B was sexually abused from the age of 10 by her alcohol-abusing father. She experienced flashbacks daily until she was 20. She was married to a dominating man at 18 and had three children at the ages of 21, 23 and 30, respectively. When she was 35, her husband had an accident, and Mrs. B took over the running of his company.

She often injured herself by hitting her head against the wall. She saw a psychologist several times for three years from 35 years of age. A physician admitted her to a psychiatric hospital when she was 37. However, she did not want to talk about her problems and never confided in any of the staff. She had 3-4 drug overdose episodes per year between the ages of 41 to 44 with multiple stays in hospital. The perceived reasons for the overdoses were her recalling childhood abuse which had long been suppressed. She was treated with lithium and Oxazepam. She was also treated with CBT from the age of 46.

She was diagnosed with PTSD and personality disorder at the age of 44 and bipolar disorder type 2 at the age of 46. She had symptoms such as flashbacks and low self-confidence. She started taking pregabalin, which replaced Oxazepam, at the age of 45. She tried to stop taking pregabalin when she was 47, but six months later her psychiatrist asked her to restart the medication because of her hyperactivity. She could not sleep well, had increased numbers of flashbacks and felt depressed. After resuming pregabalin treatment she slept better.

DSM-IV questions for abuse were negative for the last 12 months, but positive for the 12 months before that. The patient had not used any other substances to get high in the last 12 months. She became nervous at times when she did not find her pregabalin tablets.

DSM-IV questions for pregabalin dependency were negative for the last 12 months, but when asked the same questions about her situation two years ago, the patient answered positive for five of seven DSM-IV questions. She developed tolerance towards pregabalin. She had withdrawal symptoms like depression, tremors, irritability and restlessness. She did not escalate doses. She tried to stop using pregabalin without success. She spent a great deal of time obtaining and using pregabalin. She did not give up or reduce her social or occupational activities because of pregabalin.

Currently, Mrs B uses 300 mg pregabalin per day and 900 mg Quetiapine per day. She is followed up by the local psychiatric outpatient clinic.

**Case 3 (50-year male, Mr. C)**

Mr. C was bullied during childhood, but was himself also violent at home and hit his younger siblings. He married at 24 years of age. He lost his grandmother, to whom he was very close, in his early 30s and at this time he ‘lost focus’. He had several episodes of depression with passivity and suicidal thoughts. He was divorced when he was 34. At 35, he was diagnosed with severe depression and was prescribed Mirtazapine. The drug did not help and was discontinued. The depression worsened and he was admitted to a psychiatric hospital where he spent 4 months.

Mr. C got his first job as a carer for elderly people in his late thirties. At 39, he remarried. At 40, he was diagnosed with bipolar disorder. The same year he had a long hospital stay. Mr. C received Electroconvulsive Therapy [ECT], lithium, Quetiapine and Lamotrigine during this stay. In the years following this, he had two to three admissions each year due to either major depression or hypomania. Currently, he receives counseling at the outpatient clinic. Current medication consists of Quetiapine, Lamotrigine and lithium.

Pregabalin was only used during the hospital admissions for Mr. C’s anxiety. He reported little or no problem with abstinence. He first used pregabalin when he was 41 and used it until he was 47. While the use of pregabalin was high during his hospital stays, the total duration of use was not more than 30 weeks during a 6-year period.

The DSM-IV questions were asked for the last year of use which was two years ago. He scored DSM-IV negative for pregabalin abuse. Four of seven DSM-IV questions were positive for dependence. Mr. C developed tolerance towards pregabalin. He continued using pregabalin, despite knowing he had a physical problem that was probably caused by the drug. At the time of pregabalin treatment, he ended up using a higher dose than he needed.

**Case 4 (56-year female, Mrs. D)**

Mrs. D was involved in a car accident in her twenties. After this accident, she was troubled by low-grade chronic neck pain. She developed hypertension and gradually became tired. She was diagnosed with chronic fatigue syndrome at age 47. Six months later she was involved in a new car accident which exacerbated her neck problems. Her pain became unmanageable, and she became more anxious and depressed after this incident. This also led to more sleep problems.

At 53 years of age, Mrs. D was admitted to a psychiatric hospital, with symptoms of depression, tiredness and loss of appetite. She was given a low dose of Mirtazapine and Quetiapine. This did not help even with increasing dosage. Four days after admission, this medication was discontinued and Mrs. D was given pregabalin and paroxetine. Two weeks later, she was moved to a local hospital, where her dosage of pregabalin was increased to 300
mg/day. She was diagnosed with major depression and Paroxetine was increased to 40 mg/day. She was given Zopiclone treatment for insomnia. The hospital started to reduce Mrs. D’s pregabalin treatment. When she stopped using pregabalin, her symptoms, including tremor, tiredness, nausea, restlessness and tension, got worse. She could not manage the withdrawal symptoms and started to use pregabalin again. Usage continued following this episode.

None of the four DSM-IV questions for drug abuse were positive. There was no indication of other substance abuse. Only two of seven DSM-IV questions for dependence were positive, so the DSM-IV dependence criteria were not fulfilled. The questions which the patient answered positively were regarding abstinence and “failed attempts to discontinue or reduce pregabalin”. The patient originally received pregabalin for anxiety but uses it now to reduce pain.

**Case 5 (40-year male, Mr. E)**

Mr. E moved from his home in his early twenties and got a job at a computer company. His sister committed suicide at approximately the same time. Mr. E developed anxiety and depression after this. He had a history of alcohol abuse.

At the age of 35 Mr. E, was admitted to a psychiatric hospital. During this stay, he was diagnosed with GAD and severe major depression. He felt depressed, had suicidal ideas, loss of appetite, and fear of social settings. He could not talk to other people. To treat his condition, he went through several ECT treatments and was prescribed lithium and Mirtazapine. These did not help him much.

He was first prescribed pregabalin at the age of 37. The original dose was 75mg pregabalin per day which he felt did not work. He therefore increased it to 600 mg/day which he felt did not help either. Later on the dose was increased to 1200 mg/day which he finally felt helped him. He gradually started to work again at the age of 38. Mr. E has thought about reducing his use of pregabalin, but he did not want to cut it out entirely. For the two years prior to our study, he tried to stop using pregabalin for three separate periods of one day, without succeeding. He scored DSM-IV negative for pregabalin abuse, but he was pregabalin dependent according to DSM-IV. Four of seven questions for dependence were positive. He still takes 1200mg of pregabalin per day, and he is followed up by the local psychiatric outpatient clinic.

**Case 6 (22-year old female, MS. F)**

Ms. F was sexually abused at the age of 6-7 years and again when she was 18 years old. She came into contact with a youth psychiatric unit when she was 14 years old because of her problems. These were described as depression, anxiety, anger, sweating and tremors. She received Fluoxetine. She was admitted to a psychiatric hospital the same year with severe major depression. After a stay of 3 months, she was diagnosed with PTSD. During the stay, she received Alimemazine as a sedative and Venlafaxine for her depression.

From the age of 16 to the age of 18 she was admitted to hospital no fewer than 30 times. She received pregabalin when she was institutionalized but only to reduce pain and anxiety when she was an outpatient. Her sleeping problems were diagnosed when she was 17. She had a worsening of her problems when she was 18 because of the later sexual abuse episode. She was treated for weeks after that incident.

Ms. F had an accumulated pregabalin consumption of six months. She could not recall exact consumption, but she has, at times, consumed four pills per day. She does not use pregabalin now but analysis shows abuse and dependency when she was aged 17 and 18 years. One of four abuse criteria and six of seven dependence criteria for the period were positive. The only DSM-IV question which she answered negatively, was “failed attempt to reduce or discontinue” pregabalin. She had abstinence symptoms. Ms. F was troubled with serious depressions, somnolence, tremors, irritability and unrest, which she managed to cope with in the end. She uses only Escitalopram now.

**Discussion**

In total, five of the six subjects considered fulfilled criteria for pregabalin dependence either currently or previously. All five patients had psychiatric co-morbid conditions, and they were all traumatized earlier in life. Two of the subjects still had dependence on pregabalin at the time of the interview. Both of these had a history of alcohol or other substance abuse. Only two of the subjects met criteria for abuse previously, but not currently. Four of the subjects also used other psychotropic drugs. The highest daily dose of pregabalin varied between 300 mg/day and 1500 mg/day. Duration of use varied from 8 to 54 months. These findings suggest that pregabalin has addictive potential.

There are several views on the relationship between dependence and abuse, and there are several opinions about the concept of abuse. Drug abuse is, by many perceived as a less severe disorder than dependence [16]. It is widely accepted that drug abuse can lead to drug dependence. However, substances can cause dependence without abuse [17,18]. According to DSM-IV the two diagnoses cannot be used simultaneously as dependence takes precedence over abuse.

Patients with chronic disease are more or less dependent on their medication. These patients may have problems with withdrawal and other problems which might falsely be labeled as addiction. An example is described by Weissman and Haddox [19]. They used the term “pseudo-addiction” about a patient’s drug-seeking behavior which occurred because of inadequate pain treatment rather than drug dependence. The concept of pseudo-addiction is also used to describe drug-seeking behavior in conditions other than pain. Pseudo-addiction is a drug-seeking behavior which might be mistaken for dependence under DSM diagnostic criteria. This is one reason why medications for pain and anxiolytics challenge our perception of drug dependence. This may also apply for pregabalin, which is used to treat central and peripheral pain and GAD. Some of our subjects could be labeled as pseudo-addicted rather than drug dependent.

It may be difficult to get clear results in a retrospective study, but some elements in our cases suggest drug dependence. Passik et al. [20] mention a history of abuse, abuse and dependence in the same period etc. as indicators for aberrant drug-taking behavior. As shown in table 2, four of five dependent subjects had either a history of drug abuse or had been abusing and dependent at some time. These are factors that suggest true dependence, but the retrospective nature of the study and the relatively short observation time make it hard to draw definite conclusions.

However, it seems that pregabalin has potential for dependence according to DSM-IV. It causes withdrawal symptoms and tolerance amongst a non negligible number of users. These attributes make it more likely to fulfill DSM-IV criteria for dependence as only one more category needs to be fulfilled for a diagnosis of dependence (Table 1).

Pregabalin itself does not have any significant effect on the CNS reward center [7]. This challenges the drug’s abuse potential. However, some case reports and letters to editors suggest abuse [9,12,13,21]. Four percent of users experienced euphoria in a
controlled study. This supports suspicions of abuse potential. All cases so far concerning pregabalin abuse have also had a history of other substance or alcohol abuse. There is also one study which suggests that pregabalin can be abused [10]. Our findings showed that pregabalin had been abused in the past, but none of our subjects abused pregabalin at the time of the interview. This might suggest that the abuse properties of pregabalin are limited or intermittent [7].

Research shows that a significant proportion of those who meet criteria for abuse do so by fulfilling just one criterion. The most common criterion to be fulfilled by these cases is recurrent use in physically hazardous situations i.e. driving [22,23]. This is consistent with our findings. Our two subjects who had previously fulfilled the criteria for pregabalin abuse did so by only one criterion, but they were also positive for dependence. The Swedish report confirms the "history of abuse" component with most of the cases [10].

Some studies use withdrawal symptoms to give a picture of drug abuse [10,24], but according to DSM-IV this is only one of seven criteria for dependence. Meeting the withdrawal symptoms criterion alone does not suggest dependence according to DSM-IV. Withdrawal symptoms are used to diagnose dependence not abuse. It seems from this that the abuse liability of pregabalin is far lower than the dependence liability.

The method we used was a semi-structured interview where questions from MINI were included. One could have selected SCID-1 or other structured interviews, but we thought MINI would be feasible with the patient group we wanted to study. We may have missed some dependent subjects by selecting MINI, but the risk for this was reduced by history taking and additional questions.

Our study design has strengths and limitations. A case series is a descriptive study, low in the hierarchy of evidence [25]. Case series are inexpensive; take less time compared to other study designs and might have high external validity. This study design is suitable for generating hypotheses, and may be used for quantification of incidence of adverse effects. An important weakness of case series is the selection bias [25-27]. It may be that the most serious abuse and dependent subjects did not want to be a part of this study.

The study group was selected from the psychiatric outpatient population. Drug dependence and abuse are higher amongst psychiatric patients than in the general population [28]. The dependence liability and abuse pattern found for these patients might not be applicable to other patient groups.

Conclusions

The patients in the study all had severe psychiatric conditions and had been involved in multiple treatment regimes with different drugs and poor results. For all of them, pregabalin provided some help. Even if many of the patients had a history of drug abuse, pregabalin was seldom used to induce euphoria. However, on the basis of our study, we believe that pregabalin might cause dependence without abuse.

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References


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