SHORT COMMUNICATION

Tapering strips for paroxetine and venlafaxine

P.C. GROOT AND THE CONSENSUS GROUP ON TAPERING[1]

BACKGROUND Tapering strips can be used for the gradual reduction of the dose of certain types of drugs such as antidepressants and benzodiazepines. The strips contain a slightly lower dose on each consecutive day. This prevents the withdrawal symptoms still experienced by too many patients and lowers the risk of relapse.

AIM To make tapering strips of antidepressant drugs available for patients in need of a tapering-off procedure.

METHOD The Consensus Group on Tapering studied the literature and consulted with experts to find out whether the plan to make tapering strips of paroxetine and venlafaxine available for patients is feasible.

RESULTS The Cinderella Therapeutic Foundation (www.cinderella-tx.org), a not-for-profit organisation which aims to give patients access to stepchild drugs and treatments, wishes to make tapering strips of paroxetine and venlafaxine available since these are the two antidepressants that cause the most problems. The process of producing, packaging and checking the tapering doses is ISO-certified; each strip is provided with a bar-code and can be followed and traced. Therefore the strips conform to current safety regulations. In view of the large number of patients taking paroxetine and venlafaxine there is likely to be a considerable demand for tapering strips.

CONCLUSION From a financial, marketing and practical point of view, the introduction of tapering strips is feasable. Patients will derive considerable benefits. The paroxetine strips will be produced first and are expected to be available in the Netherlands from December 2013.

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KEY WORDS antidepressants, discontinuation symptoms, dose reduction, paroxetine, SSRI, tapering, tapering strips, venlafaxine

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Coming off antidepressants is in practice often harder than expected and is problematic in more than half of all cases (Van Geffen et al, 2005). This is particularly the case for antidepressants with a short half-life such as paroxetine and venlafaxine. Withdrawal of these drugs is often accompanied by the occurrence of discontinuation symptoms, sometimes very serious (see below), especially after prolonged use at higher doses.

Why gradual dose reduction is important

The main cause of these problems is that withdrawal is too rapid, which does not give the body sufficient time to adjust to the lower doses. This is why official guidelines and package leaflets rightly state that people wishing to stop taking antidepressants should do so gradually and under the guidance of their doctor (Van Weel-Baumgarten et al. 2012).

What exactly is meant by ‘gradual’ is not mentioned however and guidelines for tapering of antidepressants are lacking (Groot & van Ingen Schenau 2013).

Following recovery from depression, relapse is known to occur more often and earlier if withdrawal is rapid rather than gradual (Baldessarini et al. 2010). The magnitude of this effect is unclear. Prospective studies in the form of randomised clinical trials – which might provide an answer – have never been done and appear to be hardly feasible.

The Consensus Group on Tapering studied the literature and consulted with experts to investigate the feasibility of making tapering strips of paroxetine and venlafaxine available to patients.

DISCONTINUATION SYMPTOMS

Discontinuation symptoms are defined as the physical and mental symptoms that occur following discontinuation, interruption or too rapid a reduction of the dose of a patient’s medication. While this can happen with all types of antidepressants, symptoms are more common and more severe in the case of antidepressants with a shorter half-life. Discontinuation symptoms typically occur within 1-4 days of reducing the dose or discontinuing the antidepressant. In order to prevent these symptoms it is essential that patients are provided with careful and complete information, not only at the start of treatment but also upon its withdrawal (Vlamink et al. 2005).

Antidepressant discontinuation symptoms can be classified into 8 different groups, namely: flu-like symptoms (headache, lethargy, sweating, shivering, fatigue, loss of appetite, muscle ache); gastro-intestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea, anorexia); balance disorders (dizziness, coordination disorders); extrapyramidal symptoms (parkinsonism, akathisia, catatonia, tremor, dystonia, ataxia); psychological symptoms (agitation, irritability, worsening of mood, tearfulness, anxiety, mania, hypomania, hallucinations, delirium, aggression, paranoid delusions); sleep disorders (trouble falling asleep, nightmares, excessive dreaming, vivid dreams); sensory disorders (electric shock sensations, paraesthesia); and other symptoms (cognitive disorders, cardiac arrhythmias).

WHY TAPERING STRIPS?

For paroxetine, gradual discontinuation usually means that the dosage is reduced in steps of 5 mg down to 5 mg/day, after which the patient stops taking the medication altogether. Likewise, venlafaxine is reduced down to a daily dose of 37.5 mg/day, the lowest standard dose available at the pharmacy. It is the doctor who decides, together with the patient, how long the patient should take each subsequent dose: usually one or two weeks, sometimes longer.

Problem of unpredictability

Doctors face two problems when they help patients to taper their antidepressants. The first problem is one of unpredictability: they do not (and cannot) know which type of tapering schedule will suit which patient. While some patients manage with current schedules, it is not clear to what degree these patients suffer from discontinuation symptoms and whether their doctor gets to hear this. With other patients, current schedules fail despite rigid adherence because of the occurrence of discontinuation symptoms.

Most symptoms appear to occur during the final phase of tapering. For many patients, the step from 5 mg paroxetine to nothing and from 37.5 mg venlafaxine to nothing appears to be too big. In order to understand why this happens, we must consider the difference between the biochemical effects of antidepressants and their clinical effects, upon which the current standard dosages are based. SSRIs inhibit the reuptake of serotonin by blocking the serotonin receptor, a process that requires only very low concentrations. At such low concentrations, occupancy of serotonin receptors increases exponentially as SSRI concentrations increase (Meyer at al. 2004). Vice versa, this means that a small decrease in the daily dose leads to a very strong decrease in the occupancy of serotonin receptors, particularly if the daily dose is already below the lowest standard dose. This may explain why it is at these low doses that discontinuation symptoms are most frequently seen.

Practical problem

The second problem faced by doctors helping their patients to taper is that currently there are only limited practical options available. For paroxetine, the patient can split a pill into two or into four parts, or have the drug prescribed in liquid form, which is not practical for all patients. Venlafaxine is only available in capsules. This is why, despite a doctor's best intentions, some patients are wrongly advised to take a capsule every other day, leading to discontinuation symptoms every other day. In practice, some venlafaxine users solve this problem by opening the capsules, counting the grains within, and taking a few grains less each day. Although it is considered undesirable for patients to fiddle with their medication, this does allow patients to successfully taper their antidepressants at their own pace, sometimes over a period of months.

A final option is to first replace the antidepressant in question with fluoxetine, which has a very long half-life and therefore disappears from the body very gradually, resulting in fewer discontinuation symptoms or none at all. However, this makes discontinuation more complicated for both patients and doctors. Actually, patients are being let down because pharmaceutical companies are failing to supply the formulations needed to properly taper these drugs.

These practical problems could be avoided if patients were provided with suitable tapering strips for the final phase of withdrawal (Groot 2011; Leurink 2004). Such strips would allow tapering schedules to be more gradual and to continue down to much lower doses than is possible using the unevenly decreasing current schedules. An additional and important advantage of such strips is that they help doctors communicate with their patients. A strip for 28 days is both easier to explain to and more understandable for the patient than continually changing doses in different packings requiring several trips to the pharmacy.

It is unlikely that discontinuation symptoms will ever be completely prevented. But if patients can use suitable tapering strips these will be less frequent and less severe than during the more abrupt tapering currently practiced.

TAPERING STRIPS: TECHNICALLY FEASIBLE

A strip to taper paroxetine in 28 days from a dose of 20 mg per day requires 28 different doses, each dose slightly lower than the previous one. This can be achieved by combining tablets of different strengths, comparable to the way in which we use notes and coins for payment: each random sum of money can be paid for with a limited number of notes and coins. Similarly, combinations of only five different tablets are needed to taper paroxetine in 28 days, in very small steps. The patient takes from 1 to no more than 4 tablets per day, as is printed on each consecutive compartment of the strip.

Some pharmacists have committed themselves to personalized packaging, for example for residents of nursing homes. The pills to be taken by an individual patient are packaged by means of a fully automated process into a strip consisting of seperate compartments, each containing the medications for a specified time-point. The entire process is ISO-certified – after packaging, the pills or capsules are checked using a camera and each separate strip is provided with a barcode so that it can be followed and traced. Meeting the current safety requirements for medications will therefore not be a problem. Thanks to the automated nature of this process, it will also be possible to fill prescriptions for tailored tapering schedules. This will serve and reassure those patients who are still experiencing problems, even when they taper their medication very slowly.

THE INTERESTS OF THE PATIENT

In order to be able to produce tapering strips, a number of practical problems have to be solved. In principle the patient only needs a prescription and a pharmacist prepared to fill it. GPs are not prescribing tapering strips for their patients because they know full well that there is not a pharmacist to be found who will fill such a prescription for an individual patient. There also may be a problem with reimbursement. The reverse is also true: until GPs routinely prescribe tapering strips, pharmacists will not start producing tapering strips on a larger scale, and therefore at acceptable prices.

In 2011, almost 200,000 people in the Netherlands were using paroxetine and more than 100,000 venlafaxine (national drug consumption database (GIP)). For such large numbers of people it should surely be possible to produce tapering strips at acceptable prices. And it is not unthinkable that the use of tapering strips might eventually save our society money. We should not forget that currently much time and money is spent because of the recurrence of depression and on the discontinuation symptoms – sometimes severe – that a number of patients are currently suffering from. Many of those patients feel too ill to work, others live in fear of their depression recurring and require extra visits to their doctor.

Apart from such financial and marketing-related arguments, the most important reason in favour of introducing tapering strips is of course that they will benefit patients. Cinderella's initiative to resolve the current Catch-22 situation therefore deserves full support. Doctors are in a position to provide this support: they can help both their patients and themselves by prescribing these tapering strips as soon as they can be delivered.

NOTE

[1] On behalf of the Consensus Group on Tapering, which consists of the author and the following individuals (in alphabetical order): Baer Arts, psychiatrist, Maastricht UMC; Ton van Balkom, psychiatrist and professor of evidence-based psychiatry, dept. Psychiatry and EMGO Institute, VUmc and GGZ inGeest, Amsterdam; Aartjan Beekman, professor of psychiatry, research service GGZ inGeest/dept. psychiatry, VUmc, Amsterdam; Marc Blom, psychiatrist, healthcare director and executive, PsyQ; Tom Birkenhäger, psychiatrist, Erasmus MC Rotterdam; Bert M. van Hemert, professor of psychiatry, LUMC, Leiden; Witte J. Hoogendijk, professor of psychiatry, Erasmus MC Rotterdam; Jan van Ingen Schenau, physician, compiler of "*Silhouet literatuurservice angst en depressie*", Eerste Exloërmond; René S. Kahn, professor of psychiatry, UMC Utrecht; Ralph Kupka, professor of bipolar disorders, VUmc, and psychiatrist, GGZ inGeest and Altrecht GGZ; Roos C. van der Mast, professor of geriatric psychiatry/trainer in psychiatry, LUMC, Leiden; Willem A. Nolen, professor emeritus of Psychiatry and Emotional Disorders, dept. Psychiatry, UMC Groningen; Jim van Os, professor of Psychiatric epidemiology, Maastricht UMC; Frenk Peeters, psychiatrist, Maastricht UMC and Riagg, Maastricht; Eric Ruhé, psychiatrist-epidemiologist, dept. Mood and Anxiety Disorders, UMC Groningen and Healthcare Programme on Mood Disorders, dept. Psychiatry, AMC Amsterdam; Aart Schene, professor of psychiatry, Healthcare Programme on Mood Disorders, dept. Psychiatry, AMC, University of Amsterdam; Floor Scheepers, Department Head, dept. Psychiatry, UMC Utrecht; Robert Schoevers, professor of psychiatry and Department Head, UMC Groningen; Anne Speckens, professor of psychiatry, UMC St Radboud, Nijmegen; Jan Spijker, professor of Chronic Depression, UMC St Radboud, Nijmegen, psychiatrist, Pro Persona, Nijmegen and Trimbos Institute, Utrecht; Jan Swinkels, psychiatrist and professor of Clinical Guideline Development, AMC, Amsterdam; Ton Vergouwen, psychiatrist and trainer in psychiatry, Sint Lucas Andreas Hospital, Amsterdam; Frank C. Verhulst, professor of Child and Adolescent Psychiatry, Erasmus MC-Sophia, dept. Child and Adolescent Psychiatry and Psychology, Rotterdam.

The paroxetine tapering strips will be produced first and are expected to become available from December 2013 (the process for ordering can be found at www.cinderella-tx.org/tapering).

LITERATURE

Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid versus gradual discontinuation of antidepressants. Am J Psychiatry 2010; 167: 934-41.

Geffen EC van, Hugtenburg JG, Heerdink ER, van Hulten RP, Egberts AC. Discontinuation symptoms in users of selective serotonin reuptake inhibitors in clinical practice: tapering versus abrupt discontinuation. Eur J Clin Pharmacol 2005; 61: 303-7.

Groot PC. *Antidepressiva afbouwen. Tijd voor een andere benadering.* [Discontinuation of antidepressants. Time for a different approach.] Silhouet autumn 2011; www.vraagbaak-angstendepressie.nl/files/Groot-h11.pdf

Groot PC, van Ingen Schenau J. *Antidepressiva beter afbouwen. Pleidooi voor een richtlijn 'afbouwen van antidepressiva'. Een knelpuntenanalyse*. [Improving antidepressant discontinuation. A plea for a guideline on 'discontinuation of antidepressants'. An analysis of problem areas.] eBook. Den Haag; 2013 (download free from http://medischcontact.artsennet.nl, search term '*Antidepressiva beter afbouwen*').

Leurink H. *De medicijnontwenningsstrip*. [The tapering strip for coming off medication] NRC Handelsblad 31 Dec 2004.

Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. Am J Psychiatry 2004; 161: 826-35.

Vlaminck JJD, van Vliet IM, Zitman FG. *Onttrekkingsverschijnselen van antidepressiva*. [discontinuation symptoms of antidepressives] Ned Tijdschr Geneeskd 2005; 149: 698-701.

Weel-Baumgarten E van, van Gelderen G, Grundmeijer H, Licht- Strunk E, van Marwijk H, van Rijswijk E, et al. *NHG-standaard Depressie* (2nd revision). Huisarts en Wetenschap 2012; 55: 252-9.

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