Seroxat/Paxil fact file

Published by The Medicine Group (Education) Ltd, 62 Stert Street, Abingdon, Oxfordshire, OX14 3UQ, UK

Published in 1998

Section 3

Issues management

Chapter 1:

Managing the discontinuation issue — flexibility and control

Issue date: May 1998

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Chapter 1: Managing the discontinuation issue — flexibility and control
Introduction

- The SSRI market is becoming increasingly competitive, with both Lilly and Pfizer resorting to aggressive tactics to undermine Seroxat/Paxil's growth. Lilly are currently focusing on the issue of discontinuation, trying to turn a disadvantage into an advantage by playing to the supposed strength of fluoxetine's long half-life and active metabolites providing an in-built tapering mechanism. This is clearly a marketing ploy, already seen through by most psychiatrists, and a sign of desperation in the fight for market share.

- The purpose of this section is to position the discontinuation issue and provide a synthesis of the key facts and data in readiness for local adaptation, as required.

- The following pages provide detailed evidence to demonstrate why Seroxat/Paxil is the treatment of choice for most patients and explain its advantages throughout the various stages of therapy: initiation, continuation and stopping.

Key messages

1 Seroxat/Paxil offers the broadest range of efficacy data (including long-term) to support its position as the agent of choice in depression and depression with associated anxiety.

2 With Seroxat/Paxil, the optimal half-life of about 1 day offers flexibility and control from day 1 of therapy, unlike agents with long half-lives and active metabolites (e.g. fluoxetine).

3 With Seroxat/Paxil, the optimal 1 day half-life allows rapid washout if needed. Thus dose changes are rapidly reflected in serum levels.

4 Good clinical practice advises slow tapering of all psychoactive medications to minimize the likelihood of discontinuation events.

5 Discontinuation symptoms can occur with all antidepressants, including all SSRIs — in the case of Seroxat/Paxil they tend to occur within 2—5 days and resolve within 2 weeks. With fluoxetine, however, such symptoms may occur several weeks later and last several months.

6 Discontinuation events are not a major clinical issue, but are being used as a commercial smokescreen by Lilly in an attempt to retain market share.

7 The unique profile of Seroxat/Paxil makes it the treatment of choice, as it has benefits at all stages of the treatment course.

Background to discontinuation

The issue of discontinuation symptoms has been around for some time; however, it is only recently that Lilly have tried to turn the issue to useful commercial advantage in an attempt to arrest erosion of their market share.

Definitions

- Discontinuation symptoms are the cluster of events that can occur when a psychoactive medication is stopped abruptly.
- The syndrome should have a well defined and predictable onset, duration and offset.[1]

Terminology

- 'Discontinuation symptoms' is the preferred term for describing symptoms which may occur when an SSRI is discontinued.
- Terminology such as 'withdrawal symptoms' should be avoided as it implies dependence.
- A half-life of 1 day is 'optimal' rather than short, as it allows once-daily dosing and has inherent advantages of flexibility and control.

Facts

- Discontinuation symptoms are not a new phenomenon.
- They are well documented following the use of all psychoactive medications including:
  - MAOIs
  - TCAs
  - SSRIs (see end of section for case reports).
- Symptoms may vary depending on which class of drug is involved.[2]
- Symptoms following discontinuation of SSRIs and other antidepressants include:
  - dizziness
  - nausea
  - paraesthesia (abnormal sensations)
  - headache
  - anxiety
  - tremor
  - insomnia
  - nervousness
  - agitation
  - confusion
  - vertigo
  - vomiting.

Course

- Regardless of the frequency of occurrence, most discontinuation events following SSRI use are:
  - mild
  - transient
  - self-limiting.

- On the whole, they do not require intervention, but occasionally may be troublesome.

Management

It is good clinical practice to taper all psychoactive medications prior to stopping treatment. This greatly reduces the likelihood of discontinuation symptoms occurring.

The Lilly strategy

In a bid to regain market share, Lilly are attempting to turn the disadvantage of a long half-life into an advantage, claiming that this property provides an in-built tapering mechanism and thus avoids the potential for discontinuation symptoms. This issue has formed the focus of a number of clinical trials and presentations at key international and national congresses, as well as being the key message in sales calls. It is built upon the misleading perceptions outlined below, which are discussed in turn in the following sections.

Lilly myths

Myth 1: It is better to use a long half-life agent to avoid discontinuation symptoms and loss of antidepressant effect if a patient misses a single/multiple doses.

Myth 2: A long half-life is an advantage because it provides an in-built taper which prevents the occurrence of discontinuation effects.

Myth 3: Discontinuation effects only occur with short half-life agents. For specific rebuttals to these myths see page 16 onwards.

SB's discontinuation strategy

Continue the theme that 'all SSRIs are not the same' and focus on the advantages of Seroxat/Paxil's profile, particularly the broad range of indications, making Seroxat/Paxil the first choice antidepressant for many patients. Focus on the advantages of an optimal 1 day half-life, lack of active metabolites and the disadvantages of long half-life agents, i.e. the flexibility and control offered by Seroxat/Paxil.

Highlight the benign nature of discontinuation symptoms, rather than quibble about their incidence. Discontinuation symptoms occur with all antidepressants, and it is good clinical practice to discontinue all antidepressant therapies gradually.

The pharmacokinetic profile of Seroxat/Paxil has many advantages over that of long half-life drugs. These advantages are described in the following pages, which give advice on initiating, continuing and stopping therapy.

UK experience

Seroxat was first launched in the UK in 1991. Within 2 years of the launch, non-serious reports of discontinuation symptoms were received. A 'Current Problems' publication highlighted discontinuation symptoms following Seroxat use. This sparked off a debate in the medical literature and led to a tripling of the spontaneous reporting rate.

The Medicines Control Agency (MCA) examined the evidence for the existence of a 'serotonin withdrawal syndrome' by analysing the UK safety database of four SSRIs until July 1994. The results indicate that overall there was a low frequency of reports of discontinuation symptoms (0.002—0.3/1000). The symptoms were found to be relatively mild and, importantly, there was no evidence of habituation or physical drug dependency. [SLIDE 3]

In addition to the above analysis, data from a prescription event monitoring study also conducted in the UK indicated a very low incidence of adverse events recorded following discontinuation of SSRIs, in fact no event had an incidence greater than 0.2%.[3] It is interesting to note the higher incidence of treatment-emergent agitation and anxiety reported with fluoxetine. [SLIDE 4]

Discontinuation symptoms with Seroxat/Paxil

- Discontinuation symptoms following Seroxat/Paxil use are predictable.
- They occur within the first week of stopping medication.
- They last up to 2 weeks.
- They are unlikely to be confused with relapse or recurrence.

The perception that discontinuation events are more frequent with Seroxat/Paxil is possibly because of a combination of factors: initially inappropriate labelling of events occurring after stopping Seroxat/Paxil as being a discontinuation phenomenon when they may be the relapse of the condition; the shorter washout period (due to the optimal half-life) meaning that if such events do occur they are more likely to be associated with discontinued treatment than with fluoxetine (where they may not occur for many weeks); and the fuelling of publications and discussion on this issue by Lilly. Whilst there *are* currently a greater number of publications citing such events with Seroxat/Paxil than with other SSRIs,[4,5] the reality is that no comparative study data exist to determine the actual relative risk. Consequently, when handling this issue, the appropriate strategy is to focus on the benign nature of these events that can happen with all antidepressants rather than on the incidence.

Initiating therapy

Key considerations

When choosing an antidepressant agent the key considerations are:

- demonstrated efficacy in the condition both short- and long-term
- efficacy in comorbid/related conditions, e.g. panic disorder, OCD, social anxiety disorder/social phobia
- safety in comorbid physical conditions
- tolerability
- potential for drug interactions
- safety in overdose
- dosing convenience.

Seroxat/Paxil addresses all of these considerations in addition to offering the flexibility and control of an optimal half-life of about 1 day (see Section 1). In addition, Seroxat/Paxil has a low incidence of treatment-emergent agitation and anxiety.[3]

Pharmacokinetic considerations

Advantages of an optimal half-life agent *vs* long half-life agents during initiation of therapy include:

- starting with full therapeutic dose from day 1 for most patients
- easy titration to the optimum dose for remaining patients
- reduced time to steady state so may have a faster onset of action than agents with longer half-lives. [SLIDE 5]

Time to steady state: the optimal half-life results in a faster time to steady state than fluoxetine. [SLIDE 6]

"...delayed steady-state equilibrium results in a slower onset of action"[6]

Benefits of achieving steady state quickly

- Therapeutic levels are reached more quickly.
- Dose titration is less complicated.

The data are clear in supporting the advantages of a short half-life agent over those with long half-lives and active metabolites. There is a trend towards an earlier onset of action with Seroxat/Paxil *vs* fluoxetine in comparative studies.[6]

The benefits when initiating therapy provide powerful arguments to reinforce the advantages of Seroxat/Paxil over other agents.

In the unlikely event of an intolerable side-effect with Seroxat/Paxil, being able to stop the drug quickly is an advantage.

Continuing therapy

Key considerations

WHO and AHCPR guidelines recommend that depression therapy be continued for a period of 6—9 months in order to prevent relapse. There are, however, a number of considerations to take into account when continuing medication:

- has the agent demonstrated long-term efficacy and safety? — yes, Seroxat/Paxil (all indications); not fluoxetine
- are changes in dose readily reflected in plasma levels? — yes, Seroxat/Paxil; not fluoxetine
- does the agent offer the flexibility and control to stop if needed during chronic treatment (e.g. lack of efficacy, allergic reaction, adverse events, surgery or pregnancy)? — yes, Seroxat/Paxil; not fluoxetine
- ease of titration? — yes, Seroxat/Paxil; not fluoxetine.

Pharmacokinetic considerations

Advantages of an optimal half-life agent *vs* long half-life agents during continuation of therapy:

- there is an option for drug holidays (e.g. for sexual dysfunction, or need for surgery) with no loss of efficacy
- any dose change is quickly reflected in plasma levels, unlike fluoxetine, which can take more than a month to reach a new steady-state concentration after an adjustment in dosage.[7]

Drug holidays

Sexual dysfunction is a class effect of SSRIs that can lead to non-compliance. Clinical studies show that some drugs can be stopped for 2 or 3 days to allow normal sexual function to be restored in patients who are affected. There is no loss of efficacy, and discontinuation effects do not appear during this time.[8] This is not possible with long half-life agents such as fluoxetine because plasma levels remain high for some time after stopping medication. [SLIDE 7]

Stopping medication

Key considerations

- Is the patient better?
- Is the patient suffering from serious adverse events?
- Is the medication not working, so the patient needs to switch?
- Does the patient need surgery?
- Is the patient pregnant and does she want to avoid exposing the foetus?

The doctor and patient need to keep control of therapy to allow them to stop/change swiftly as the situation requires.

Pharmacokinetic considerations

Advantages of an optimal half-life agent *vs* long half-life agents when stopping therapy include:

- time to washout is shorter, with important implications in cases of switching or pregnancy
- potential for drug interactions after stopping is minimized
- discontinuation events (if they occur) are predictable, as they occur a short time after stopping and the duration of these events is short.

Time to washout

In about 40% of cases, it is possible that the patient will need to switch medication. An optimal half-life agent gives the physician the flexibility to change drugs rapidly. Seroxat/Paxil makes it easier to manage patients as dose changes are quickly reflected in plasma levels. Long half-life agents like fluoxetine do not permit this flexibility because they take so long to be washed out (the active metabolite of fluoxetine, norfluoxetine, has a half-life of 4—16 days). The graph opposite[9] [SLIDE 8] represents mean values and washout may take up to 4—5 times the half-life.

Implications of slow clearance of fluoxetine:

- Even in an emergency situation, the drug cannot be stopped immediately as neither fluoxetine nor norfluoxetine can be cleared, even with:
  - — dialysis
  - — forced diuresis
  - — exchange transfusion
  - — haemotransfusion.
- Active drug (fluoxetine and norfluoxetine) may remain in the body for an extended period following discontinuation.

Case/Reference	Fluoxetine/norfluoxetine blood levels
Coplan and Gorman (1993)[10]	84 ng/ml norfluoxetine 9 weeks after stopping fluoxetine.

	Concentration is equivalent to steady-state levels for a person stabilized on therapeutic dose of fluoxetine.
Pato *et al.* (1991)[11]	Clearly detectable levels of fluoxetine (55 ± 19 ng/ml) and norfluoxetine (184 ± 40 ng/ml) found at 4 weeks post discontinuation. After 8 weeks, norfluoxetine still detected.
Vandel *et al.* (1994)[12]	Measurements made up to 60 days after fluoxetine discontinuation. Half-life of fluoxetine varied from 8—56 days, norfluoxetine 9—40 days.
Burke *et al.* (1996)[13]	Fluoxetine still detectable in plasma for 3 weeks and norfluoxetine for 7—11 weeks after stopping fluoxetine. After 3 weeks post-dose, norfluoxetine plasma levels remained at one-third steady-state values.
Dominguez *et al.* (1996)[14]	Norfluoxetine still detectable in plasma 4 weeks after stopping fluoxetine. After 2 weeks post-dose, norfluoxetine plasma levels were 40% of steady-state values. Norfluoxetine half-life was over 11 days.

Potential for drug interactions

"At least 5 weeks should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI" Prozac prescribing information

- The potential for drug—drug interactions persists for longer with long half-life agents.
- Beasley[15] reported 7 deaths in patients who had taken MAOIs concurrently with, or after stopping, fluoxetine.
- Plasma desipramine levels remained significantly elevated for more than 3 weeks after discontinuation of fluoxetine.[16]
- As specified on product labelling documents, only 2 weeks (1 week in France) need elapse between discontinuation of Seroxat/Paxil and start of an MAOI.

The SSRIs differ in their effects on cytochrome P450 isoenzymes. Seroxat/Paxil has a limited and very well-defined interaction liability and, therefore, has less potential for unexpected drug—drug interactions. In cases where there is a theoretical risk of potential interaction, the new drug can be started more quickly after stopping Seroxat/Paxil than after stopping fluoxetine. Conversely, with fluoxetine the physician (and the patient) will need to wait at least 5 and up to 12 weeks before the potentially interacting drug can be taken safely. There is also the risk that with fluoxetine you could

get an interaction when not expecting it — patients may not realise that fluoxetine and norfluoxetine are still in the body many weeks after stopping, and take a potentially interactive agent.

Pregnancy

> *"Discontinuation of agents such as...paroxetine at the onset of gestation allows for a rapid washout of drug and metabolite."*[17]

While there is no evidence that any of the SSRIs causes problems in pregnancy, a 1 day half-life gives the physician and the patient the flexibility to choose whether or not to continue to expose the foetus to the drug. In contrast, fluoxetine and its metabolite even if stopped immediately after conception, will still be detectable at the end of the first trimester. Seroxat/Paxil minimizes the risk by enabling rapid clearance if necessary.[17] This gives the doctor and the patient control and flexibility to make the most appropriate treatment choice.

Summary of features and benefits of Seroxat/Paxil at different treatment stages

Treatment stage	Features	Benefits
Initiation	• Efficacy across wide range of indications	• Suitable for all patient types, particularly those with anxiety symptoms
	• Rapidly reaches steady state	• May indicate trend to early onset of action
	• Safe and well tolerated	• Low dropout rate due to side-effects
	• Simple dosing	• Good patient compliance
Continuation	• Long-term efficacy and relapse prevention	• Minimizes use of healthcare resources due to relapse
	• Simple and convenient dosing	• Aids compliance
	• Minimal concern with drug interactions	• Suitable for use in patients with concomitant illness; elderly
	• Safe and well tolerated	• Management of serious overdose possible
		• Low dropout rate due to side-effects
	• Optimal 1 day half-life	• Dose changes quickly reflected in plasma levels
Stopping	• Optimal 1 day half-life	• Flexibility and control to stop quickly if needed
	• Short washout	• Duration of (discontinuation) adverse events minimized
		• If they occur, discontinuation events happen predictably soon after stopping — not confused with relapse
		• Can safely start other medication, e.g. MAOI, after 2 weeks (c.f. 5 weeks for fluoxetine)

Managing discontinuation

It is widely acknowledged that discontinuation symptoms can occur with all classes of antidepressants if stopped abruptly (see following case list for examples). All psychotropic drugs (no exceptions) should, therefore, be discontinued gradually. In all cases the following steps should be followed:

- educate the patient — emphasize the importance of taking the drug every day and continuing until told otherwise by the clinician
- taper the dose
- if symptoms appear, restart treatment and proceed with downward titration more slowly.

Equally critical is to ensure that there is no confusion between discontinuation symptoms and the withdrawal symptoms commonly associated with dependence-forming agents like the benzodiazepines. SSRIs are not addictive.

"There is no evidence to suggest that paroxetine is associated with either physiological or psychological dependence."[18]

"Prescription-event monitoring found no evidence of physiological or psychological dependence in patients treated with paroxetine; there were no reports of tolerance, craving, drug-seeking behaviour or self neglect."[18]

SSRI case reports

The following case reports provide evidence of discontinuation events with SSRIs other than Seroxat/Paxil.

SSRI	Report	Case summary
fluoxetine	Kasantikul, 1995[19]	Elderly patient developed visual hallucinations, disorientation and confusion 2 days after stopping fluoxetine
	Einbinder, 1995[20]	Patient suffered from fatigue 2 days after discontinuing fluoxetine. A further attempt to stop treatment led to the emergence of dizziness after 9 days
	Stoukides and Stoukides, 1991[21]	Extrapyramidal symptoms appeared 2 days after stopping fluoxetine
	Berlin, 1996[22]	Three cases of withdrawal symptoms in which vertigo and/or dizziness persisted for up to 8 weeks after fluoxetine withdrawal
sertraline	Louie *et al.*, 1994[23]	Fatigue, severe abdominal cramps... 'flu-like symptoms appeared 2 days after abrupt discontinuation of sertraline. Symptoms remitted when sertraline restarted
	Leiter *et al.*, 1995[24]	Two cases reported — first patient complained of fatigue, irritability, slowed thinking and a constant tingling under the skin surfaces 2 days after stopping sertraline. Second patient suffered 'flu-like symptoms, loss of balance and burning and tingling. In both cases, symptoms remitted 2 weeks post discontinuation
fluvoxamine	Szabadi 1992[25]	Patient tried to discontinue fluvoxamine on becoming pregnant. She claimed she could not stop, as when she had tried before she was overwhelmed with feelings of aggression
	Mallya *et al.*, 1993[26]	Symptoms suggestive of a withdrawal effect were documented in four patients discontinuing fluvoxamine, immediately after the dose was tapered. Patients complained of constant headaches, dizziness, nausea and chest tightness

Rebutting the Lilly myths

The thrust of the Lilly myths has already been addressed in the preceding pages, but the following section summarizes the points that refute the three main attacking points used by Lilly against Seroxat/Paxil.

Myth 1: *It is better to use a long half-life agent to avoid discontinuation symptoms and loss of antidepressant effect if a patient misses a single/multiple dose.*

- A single missed dose will not result in discontinuation symptoms nor loss of antidepressant effect — as borne out by the successful use of drug holidays with Seroxat/Paxil.[8]
- Initiating treatment with a drug with a long half-life and active metabolites immediately removes control and flexibility in the event of:
  - unexpected or severe side-effects
  - the need to switch to an alternative medication
  - pregnancy
  - potential drug interactions.
- Physicians should encourage patients to comply, and warn them of the dangers of non-compliance. SB is committed to improving patient compliance through its patient and physician education programmes.

Myth 2: *A long half-life is an advantage because it provides an in-built taper which prevents the occurrence of discontinuation effects.*

Implications of slow clearance of fluoxetine:

- Discontinuation effects happen with fluoxetine — they just take longer to occur and last longer (so can be confused with relapse/other conditions); see Myth 3.
- Active drug (fluoxetine and norfluoxetine) may remain in the body for prolonged periods (about 5 weeks) following discontinuation, maintaining the potential for drug—drug interactions.
- In the event of an emergency, it is impossible to remove fluoxetine/norfluoxetine from a patient. Neither fluoxetine nor norfluoxetine can be cleared, even with dialysis, forced diuresis, exchange transfusion or haemotransfusion.

Myth 3: *Discontinuation effects only occur with short half-life agents.*

Discontinuation symptoms following fluoxetine use are well documented:

- due to its pharmacokinetic profile, symptoms may occur up to several weeks later as only at that stage is the drug cleared from the body[22]
- symptoms may last for several weeks[22]
- symptoms are more likely to be confused with a relapse/recurrence of the original disorder
- symptoms may be misdiagnosed as a new condition, leading to inappropriate investigations and increased use of healthcare resources.

The fluoxetine trials

Discontinuation symptoms with fluoxetine

SB conducted a placebo-controlled trial to assess the tolerability of an immediate switch from a stable dose (6 weeks) of fluoxetine to Seroxat/Paxil in depressed patients.[27]

Protocol

One group of patients switched directly to Seroxat/Paxil (n=123), the other to placebo (n=119). Those patients switched to placebo were, in effect, being abruptly discontinued from fluoxetine. Adverse events were monitored weekly over a 2-week period.

Results

The results demonstrate evidence of discontinuation-like symptoms occurring within the 2 weeks following abrupt cessation of fluoxetine treatment. These symptoms would have been likely to increase in incidence if the patients had been followed long-term. [SLIDE 9]

Lilly demonstrate discontinuation symptoms with other SSRIs

Lilly performed a study in depressed patients who were switched from fluoxetine, sertraline or Seroxat/Paxil to placebo for about a week. This study was presented at the APA and WCBP congresses in 1997, 2 years after publication of the above study, to show that fluoxetine had no discontinuation events. The study was in fact deliberately designed not to detect the discontinuation effects associated with long half-life drugs. Discontinuation symptoms, if any, will appear with Seroxat/Paxil on average 3—4 days after stopping; with fluoxetine it can take 6 weeks or more.

Protocol

Lilly conducted this trial in the US and designed it specifically to look at the incidence of discontinuation events following a 5—8 day interruption of treatment with fluoxetine, sertraline or Seroxat/Paxil.

- It included 191 patients successfully treated for major depression over a period of 4—24 months.
- Patients received placebo substitution for 5—8 days at week 2 or 3.
- Patients were monitored for 1—2 weeks following resumption of active drug therapy.

Results

Not surprisingly, patients exhibited significantly more adverse events with sertraline or Seroxat/Paxil than with fluoxetine during the short follow-up period following discontinuation of

therapy. Lilly claim that the results show a reduction in antidepressant efficacy of the short half-life SSRIs and the onset of discontinuation symptoms.

Flaws and failings in the Lilly study

Flaw: The study design has a treatment break of 5—8 days. This is not relevant to the real world as it is unlikely patients would miss 1 week of treatment and then start again. A more realistic time period would have been 2—3 days, which Rothschild has shown to have no effect on symptoms of depression.[8] In addition, the ethics of such a study have to be called into question, in terms of the impact of disrupting therapy in depressed patients who are already stabilized.

Failing: The study failed to detect any signs of discontinuation with fluoxetine because it did not follow patients for long enough afterwards (only 1—2 weeks). The long half-life of fluoxetine means that it can take up to 80 days to clear the active metabolite from the body.

Flaw: Patients were not assigned randomly to the study — the groups of patients were not comparable.

Failing: The study failed to blind patients completely. Patients and physicians alike knew which product they were taking when treatment interruption took place. This can influence the results significantly.

Failing: The placebo-controlled group was ignored in the analysis, thus undermining the validity of the study.

Flaw: The method used to collect adverse events — a checklist — over-inflated the findings and the difference between the treatment groups.

Flaw: The scales used to measure adverse events — the Discontinuation-Emergent Signs and Symptoms (DESS) and the Symptom Questionnaire (SQ) — are not validated scientific tools. Lilly have created these instruments to suit their own purposes.

Conclusion

Studies are normally designed to answer a hypothesis in a scientific, well-controlled manner. The design of the Lilly study was fundamentally flawed and answered no particular questions. The results are rendered uninterpretable and, therefore, invalid. It is impossible to draw any meaningful conclusions from the study.

Lilly's own data show fluoxetine discontinuation events

Ironically, a trial presented by Lilly at APA in 1997 actually demonstrated discontinuation events on stopping fluoxetine!

Protocol

- Patients stabilized on fluoxetine were randomly assigned to either placebo or continued on fluoxetine in a double-blind fashion.
- Patients were followed over the next 6 weeks.
- Patients were asked about adverse events using an open-ended questionnaire.

Results

- At weeks 4 and 6, patients randomized to placebo (i.e. abruptly discontinued from fluoxetine) showed a statistically significant increase in incidence of dizziness.
- Results support the appearance of discontinuation effects at the point when fluoxetine is washed out of the body.

Even a speaker at one of the Lilly meetings focusing on this issue has recently published an article in the BMJ stating that antidepressant discontinuation reactions are preventable and easy to treat.[28]

Discontinuation — conclusions

The issue of SSRI discontinuation has been almost entirely driven by marketeering and is often based on misinterpreted or carefully selected data. Although the short half-life SSRIs appear to be most often cited in case reports, discontinuation reactions have been reported for all SSRIs and symptoms are generally mild and of short duration. The severity of symptoms does not appear to be related to either dose or treatment duration, but to abrupt discontinuation.

The purported disadvantage of the shorter half-life SSRIs is counterbalanced by disadvantages of the long half-life SSRIs. When one wishes to stop medication abruptly, for whatever reason, the shorter half-life SSRIs with no active metabolites offer the better option.

It is important to educate patients and practitioners alike not to stop antidepressant medications abruptly. In fact, virtually all psychotropic agents, including SSRIs, TCAs, benzodiazepines, lithium and antipsychotic drugs, should be tapered off gradually.

As seen on the preceding pages, Seroxat/Paxil has advantages over fluoxetine at all stages of therapy — initiation, maintenance and when stopping. This is why Seroxat/Paxil is becoming the

number 1 antidepressant around the world (and why Lilly are desparately trying to use this issue to turn their disadvantage of a long half-life into an advantage.

Sharing best practice

USA

A leave-piece highlighting the benefits of the optimal 1 day half-life of Seroxat/Paxil in comparison to fluoxetine. Key points it raises include:

- Seroxat/Paxil has no active metabolites
- Seroxat/Paxil has a short elimination half-life
- Seroxat/Paxil has a short washout period, giving flexibility and control. [2 FIGURES]

Netherlands

A specific detail aid describing the advantages and disadvantages of both short (17 hours or less) and long (36 hours or more) half-life agents. The centre panel, in the form of an overlay, describes the advantages and sole disadvantage of optimal half-life agents (17—36 hours).

A translation is provided below.

Optimal half-life of 24 hours[13]

- Simple once-daily dosing[1]
- Interactions can be quickly corrected[1]
- Adverse events can be quickly reversed[1]
- Fast onset of response[12]

(Centre panel) Optimal $t_{1/2}$ (between 17 and 36 hours)

- switching free of problems[1]
- guarantee continuity of therapy[2,3]
- if necessary it is possible to stop therapy immediately (e.g. pregnancy, allergy, serious adverse events)[1]
- steady state quickly reached[1,4]
- less chance of breakthrough symptoms if a dose is missed[2]

- greater risk of discontinuation symptoms.[5]

(Left panel) The facts about antidepressant half-lives:

Advantages of a short $t_{1/2}$ (< 17 hours)[1]

- no problems with switching[1]

- it is possible to stop therapy immediately if necessary (e.g. pregnancy, allergy, serious adverse events)[1]
- steady-state achieved quickly.[1,4]

Disadvantages of a short $t_{1/2}$

- greater risk of discontinuation symptoms[5]
- non-compliance may lead to a less effective therapy or to relapse[7]
- multiple daily dosing.

(Right panel) Advantages of a long $t_{1/2}$ (>36 hours)[1]

- guaranteed continuity of therapy[2,3]
- less chance of breakthrough symptoms if a dose is missed[2]
- once-daily dosing.[1]

Disadvantages of a long $t_{1/2}$

- switching to avoid interactions is difficult[4]
- stopping therapy immediately is not possible (problematic in case of pregnancy, allergy or serious adverse events)[4,6]
- interactions can occur long after therapy is stopped (beyond duration of pharmacists, pharmacovigilance system)[3,6]
- possible slow onset of response (time until steady-state is long)[1,8]
- late-occurring adverse events may not be recognized as such[3,7]
- difficulty with dose titration[9,10]
- chronic use: greater risk of toxicity by accumulation, especially with renal/hepatic impairment[3,6]
- challenge testing of adverse events is difficult[3]
- managing serious overdose is difficult.[11]

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France

A page from the French detail aid describing the simple pharmacokinetics, lack of active metabolites and rapid washout of Seroxat/Paxil. [FIGURE]

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