

Original Article

COMPARISONS BETWEEN PSYCHOTROPIC DRUGS: MUST THE RISK OF SIDE EFFECTS DICTATE OUR PRACTICES?

N. Zdanowicz, D. Jacques, C. Reynaert

Key words: antidepressants, neuroleptics, anxiolytics, efficacy, side effects, cost-effectiveness.

ABSTRACT

Objectives: Recently, SOHO and CATIE's studies in the field of schizophrenic disorders asserted that molecules apparently showing the most side-effects are not only the most effective but also lead to the least changes in treatments. Can we generalise this assertion to other domains of pharmacological treatments, such as in mood and anxiety disorders? And, more generally, do we possess information about comparison between different types of molecules in these different fields. **Methods:** Review of the literature (medline – psycinfo – psycarticles) addressing these three psychiatric disorders, and comparing efficacy of treatments, or cost-effectiveness studies. **Results:** Although there is a plethora of publications about the efficacy of given molecules

vs. placebo, studies comparing molecules are scarce, and studies on cost-effectiveness in natural environments are even more scarce. Independently of the type of disorders under study, the last few years' efforts to completely limit side effects seem to have resulted in a loss of efficacy. Moreover, the previously held hypothesis suggesting that the fewer the side effects, the lesser the need to change treatment has not been confirmed. The duration of a treatment is more dependent upon its efficacy than on other variables. **Conclusions:** Clinicians cannot determine the absence of noxiousness of a molecule as their primary criterion of choice. In contrast, they should carefully balance side effects and efficacy. In Psychiatry, there is a lack of studies about cost-effectiveness in natural environments.

Université Catholique de Louvain;
Psychopathology and Psychosomatic unit;
Cliniques de Mont-Godinne,
Yvoir, Belgium

Address for Correspondence:
Professor N. Zdanowicz, MD, PhD
Médecine Faculty
Université Catholique de Louvain
Psychopathology and Psychosomatic unit
Cliniques de Mont-Godinne
5530 Yvoir
Belgium
Tel: +32 (0)81 42 37 51
Fax: +32 (0)81 42 37 51
E-mail: nicolas.zdanowicz@uclouvain.be

INTRODUCTION

If the maxim "primum non nocere" has dominated our thinking for quite some time, it has become an established rule since the 1990s. While tracing this development is beyond the scope of this paper, we just wish to remind readers that this maxim articulates a specific historical context, which includes ecological concerns to filing lawsuits against healthcare professionals by way of the "principle of security". Thus, while we will not discuss the relevancy of this trend, it seems to have been, at times, taken to disturbing extremes. For example, in the field of pharmacotherapy, some molecules (a COX 2 for example) were withdrawn from

the market because of suspected side or even lethal effects, without considering their contribution to the improvement of the conditions of thousands of suffering patients. In psychopharmacotherapy, the most striking example of this trend is the suspicion that antidepressants provoke suicide (1). This suspicion led some psychiatrists to wonder if prescribing SSRIs (Selective Serotonin Reuptake Inhibitors) was not equivalent to prescribing a "suicide antidepressant inductor" (2). The emergence of "clean" antidepressants (i.e. acting on one type of receptors) in the early 1990s, as well as the promotion of this "cleanliness", particularly in terms of the small number of side effects, has certainly contributed to this extreme situation.

The label "low in side effects" was promoted differently for anti-depressants and anxiolytics on one hand, and for neuroleptics on the other. In the case of antidepressants and anxiolytics, this claim of reduced side effects was immediately associated with high selectivity. Conversely, neuroleptics have been made "dirtier" while losing selectivity on dopaminergic receptors on behalf of a dopamine/serotonin balance. Considering these opposite techniques, one nevertheless wonders if these "progresses" have not resulted in a loss of efficacy. While antidepressants show the progressive return of "dirty" molecules, the "new molecules" in anxiolytics have never targeted benzodiazepines (BZD) in acute conditions, and research efforts are reduced to try and prove their long-term efficacy. Finally, SOHO (Schizophrenia Outpatient Health Outcomes), and CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) studies have recently revealed that it is the efficacy of a treatment rather than reduced side-effects that best explains physicians' and patients' adherence to some neuroleptics over others. Thus, second generation neuroleptics, which produce the highest level of side effects, also proved to be the most efficient. In summary, the objective of this paper is to explore whether similar patterns also exist in others fields of psychopharmacological treatments, such as mood and anxiety disorders, and more generally, to assess whether we possess information about comparisons between different types of molecules in these different treatments.

METHODS

To reach this objective we conducted a review of the literature with 3 tools: medline – psycinfo – psycarticles, using the keywords "compare*", "effect*", "cost effec-

tiveness" within the 3 fields of: (a) psychosis, schizophrenia or neuroleptics, (b) depression or antidepressants; and (c) anxiety, panic, or anxiolytics. We excluded all the papers where we could only find comparisons between placebo and one molecule.

NEUROLEPTICS

CATIE's research (3) was motivated by the authors' questioning the validity of the promise of higher efficacy and safety of second generation neuroleptics in comparison to the first one. According to them, research publications until now have shown neither consistency nor robustness, except for clozapine. A recent study by Jones et al (4) even suggests that the quality of life associated with first generation neuroleptics is higher than with second generation neuroleptics. Finally, according to CATIE's authors, results from studies on improvement of mood symptoms and cognitive decline do not allow drawing clear conclusions in favour of second generation neuroleptics. It should nevertheless be noted that this last remark is contradicted by Peuskens and Thibaut's review of 2005 (5).

The design of the above two studies slightly differed from each other. Both were conducted in natural environments (ambulatory patients consulting their psychiatrists). SOHO's study included 7,000 schizophrenic patients, who were observed over a period of three years, whereas CATIE's research included 1,493 patients, who were studied over a period of 18 months. In CATIE's study, patients were equally randomised for the different molecules. SOHO's study included two equally distributed cohorts of patients, one treated with olanzapine, and the second with another 2nd generation neuroleptic. The choice of the initial treatment was made by the clinicians. In terms of dosage, prescription of 2nd generation drugs in both studies were roughly similar, except that in CATIE's study, per day, prescriptions of olanzapine ranged from 7.5 to 30 mg (20.1 mg average prescribed dose), and more classically averaged 11.8 +/- 6.2 mg in SOHO's study. Apart from this exception, maximal and minimal doses corresponded to the quantities that were recommended by the different pharmaceutical companies, and intermediary dosages were left at discretion of the clinician (example of doses per day prescribed in CATIE's study: quetiapine ranged from 200 to 600 mg [average prescription = 543.4 mg], risperidone ranged from 1.5 to 6 mg [average prescription = 3.9 mg], ziprasidone ranged from 40 to 140 mg [average prescription = 80 mg]; amisulpride was

only prescribed in the CATIE's study at the average dose of 407 mg). In CATIE's study, comparisons between 1st and 2nd generation drugs were performed through the administration of only one neuroleptic of the 1st generation which served as a reference: perphenazine, whose prescription ranged from 8 to 32 mg daily (average prescription = 20.8 mg). In SOHO's study, 1st and 2nd generation drugs were compared through the administration of 12 different 1st generation neuroleptics oral, and IM long action (deposit form). In those cases where the first molecule was stopped (by the psychiatrist or by patient's initiative), the clinician chose another neuroleptic, in the same dosage as in phase 1 of the experiment in order to comply with the experimental deadline-target. Moreover, during the second phase of CATIE's study (6, 7), prescribing doctors could recommend clozapine (at the average daily dose of 332.1 mg).

Like the first large scale studies of the influence of environmental factors on schizophrenia, the results of CATIE's and later SOHO's studies left their mark on psychiatry for the following reasons:

1. They did not highlight the superior efficacy of 2nd generation neuroleptics, except for those which show the highest level of side-effects.
2. They showed that adherence to treatment (patients interrupting it on their own, or the treatment being changed by MD's) was very low, and that the presence of additional side-effects did not affect changes in treatment.
3. Finally, they reported considerable differences in satisfaction with treatment among clinicians and patients.

1. In terms of decrease in psychopathology, duration of successful treatment, and rates of re-hospitalisation, both studies found that clozapine, and olanzapine were the most effective 2nd generation molecules, even when compared to first generation ones. Nevertheless, in the second phase of CATIE's (6) study, risperidone proved to be as efficient as olanzapine with even a slightly longer treatment adherence. This positive result of risperidone was reproduced in SOHO's study, where it correlated with the same low risk of rehospitalisation as olanzapine versus all other molecules. On the whole, the other molecules were comparable with each other in terms of efficacy, with perphenazine (1st generation neuroleptic of reference in the study) having proved as "good" as risperidone, ziprasidone or as quetiapine during the first phase of the CATIE's study.

Another analysis of CATIE's study (8) was conducted from the statistical standpoint of "Number Needed to Treat" (NNT – the number of patients to treat in order to have one positively responsive patient), and "Number Needed to Harm" (NNH – the number of patients to treat in order to have one patient reporting side effects). While NNT analysis did not bring any new information, NNH analysis suggested a higher tolerance profile for risperidone, and a better metabolic profile of ziprasidone. These last results confirm Breier et al⁹ (published at the same time as CATIE's study) who compared olanzapine to ziprasidone over a period of 28 weeks.

The results of SOHO and CATIE's comparative studies between 1st and 2nd generation neuroleptics must certainly be qualified in terms of the first generation neuroleptic they used as a reference for comparison. Unfortunately, an analysis comparing the various 1st generation molecules of SOHO's study (where they were all included in the same group of comparison, under the label: "1st generation") has not yet been conducted. However, previous studies point to some variations. For example, a comparison between haloperidol and risperidone (10) among 397 patients points to more efficacy, less side effects, and a much longer period of adherence (364 days versus 238). The meta analysis of Leucht et al (2003) (11) found lower rates of relapse for olanzapine, sertindol, and risperidol than with haloperidol. In this study, clozapine proved disappointing, with results that were comparable to those of haloperidol, noticeably, in terms of relapses, but also in terms of increasingly serious side effects (aplasia). In this study, no neuroleptic was found to be superior than haloperidol in terms of side-effects.

On the whole, when comparing the efficacy of 1st and 2nd generation of neuroleptics, three groups of 2nd generation neuroleptics can be distinguished. In the first group, which includes 2nd generation neuroleptics that are clearly superior to the 1st generation, one finds clozapine. The second group (same efficacy) includes amisulpride, risperidone, and olanzapine, and the third group (less efficacy) contains aripiprazole, quetiapine, sertindole, and ziprasidone.

2. The speed at which the treatment was stopped in CATIE's study was catastrophic, and only slightly better in SOHO's study. In CATIE's study, a total of 74% of treatments were prematurely interrupted whereas "only" 40% of the treatments in SOHO's study were changed in a similar time period. However – and this is a significant

point – the 2nd generation neuroleptic that was most criticised for its side-effects – olanzapine – was also the one that had the lowest rate of interruption in both protocols. Compared to olanzapine, the authors found only one molecule with better results, clozapine, whose relative risk (RR) of interruption is estimated at 0.82. The following molecules were –in descending order–: risperidone (RR SOHO: 1.28), the first generation molecules in the form of deposit (only tested in the SOHO's experiment, RR: 1.43), amisulpride (only tested in the SOHO's experiment, RR: 1.63), first generation neuroleptics per os (RR: 1.7), ziprasidone (only tested in the CATIE's experiment), and quetiapine (RR: 2.22). In both studies, the insufficient control of positive symptoms was a decisive factor for abandoning the treatment.

3. The speed at which treatments were interrupted (CATIE) because of side-effects is globally equivalent for all molecules, but the rate of interruption for a specific reason varied from one molecule to the other. Thus, olanzapine was discontinued because of its side-effects on body weight, or because of its metabolic effects, whereas perphenazine was discontinued mainly because of extrapyramidal symptoms. Although in the second phase of the CATIE's experiment, treatment was also interrupted in 74% of the cases but risperidone showed the longest durations of adherence (7 months), as compared to olanzapine (6.3 months), and ziprasidone (2.4 months).

The most meaningful observation found in CATIE's study was the difference between patients' subjective satisfaction with their treatment, and the clinicians' objective assessment of patients' improvement, this was also found in the meta analysis by Liu-Seifert et al (12). This analysis included 1627 patients suffering from schizophrenia, or related disorders (schizophreniform or schizo-affective disorders), who, during a 24-28 weeks double blind trial, received either olanzapine (10-20 mg), risperidone (4-12 mg), quetiapine (300-700 mg), or ziprasidone (80-160 mg). As in the CATIE's study, the rate of stopping the treatment was very high: one out of two patients stopped treatment prematurely. One third of the patients mentioned the lack of efficacy, and 12% complained about side effects (putting on weight was only mentioned by 0.2%). While the lack of efficacy mentioned by patients was partially confirmed by the lack of improvement as observed through the PANSS (Positive And Negative Syndrome Scale), the negative response to treatment was statistically more salient in the patients' subjective perception than in the clinicians' observations (80% vs 20%).

Naber et al (13) studied 144 patients, who were treated for 26 weeks and found even a negative correlation between the patients' subjective improvement and the levels of improvement observed by clinicians through the PANSS. Thus, if as in the CATIE's study, we observe that the continuation of a treatment is determined by a good (subjective and objective) response to it during the first two weeks (80% of these patients continued this experiment until its end), one must notice that the respondents who discontinued their treatment because of side-effects did not necessarily do so because of serious symptoms. These "drop-outs" could have been equally "good" respondents as those who complete the trial. According to Day et al (14), the quality of the doctor-patient relationships is the most important variable determining the patient's attitudes toward the medical treatment.

ANTIDEPRESSANTS

Although SSRIs have been prescribed for quite some time, most studies comparing the efficacy of tricyclic antidepressants (TCA) with SSRIs are as recent as the comparative studies between the 1st and 2nd generation neuroleptics. On the other hand, since the prescription of antidepressants concerns more the primary care setting, we can find some studies that do investigate this topic. The other major difference is that, compared to 2nd generation neuroleptics, SSRIs were not presented as being more efficient than TCAs, but only as producing less side-effects, and after just one intake, a better compliance.

Peveler et al¹⁵ conducted a large scale study in the ambulatory setting over a period of one year. Seventy three general practitioners followed three groups of patients (N total = 327). In the TCA group, patients were prescribed amitriptyline, dothiepine, and imipramine; in the SSRI group, patients were prescribed fluoxetine, sertraline, and paroxetine, while in the third group lofepramine was prescribed (a molecule close to desipramine). Patients were regularly assessed through the HAD-S (Hospital Anxiety and Depression Scale). The conclusions of this study can be summarized as follows:

- Patients' compliance was barely better than those taking neuroleptics: although 68% were still taking their medication three months after the beginning of their treatment, 52% of the patients discontinued it after a year.

- No difference was found between the three groups, neither in the analysis of the number of weeks without depressive symptoms, nor in the analysis of costs per week without symptoms.
- The only analysis that suggests a slight SSRIs advantage is a cost-effectiveness analysis over a year.

The same year, a meta-analysis of first line patients studies was published¹⁶ in which the authors claimed to have found only 10 TCA-placebo comparative studies, 3 SSRIs-placebo studies, and 2 TCA-SSRI-placebo studies. The four main criteria of analysis that were retained were: differences in scores of depression by the end of the treatment, the relative risk of improvement, the NNT, and the NNH.

In addition to the limited number of studies, and their short duration (6-8 weeks on average), the authors first observe that both types of molecules are more efficient than placebo --with a level of 9% to 18% more responsive patients ! This finding challenges the assertions written in the *folia pharmacotherapeutica* (1) from March 2006 about the inefficacy of antidepressant drugs. Although, when compared to placebo, the response to SSRIs proved to be slightly more efficient with a relative improvement of 1.37 (95% CI, 1.21-1.55) versus 1.26 (95% CI, 1.12-1.42) for the TCAs, the NNT did not support the use of SSRIs. Six patients on SSRIs, and four patients on TCA are needed to obtain one responsive patient. NNHs vary considerably from 5 to 11 for TCAs, and from 21 to 94 (I) for SSRIs. These results partially contradict those suggested by one of the first meta-analyses, (17) which reported that the number of patients who remained responsive until the end of the research was superior with TCAs than with SSRIs, but also that the number of patients who discontinued taking TCAs because of side-effects or lack of efficacy was higher than among patients taking SSRIs. The conclusions these two groups of authors reached were akin to synthesis of Butler et al published in 2005 (18). Antidepressants are statistically more effective among patients suffering from moderate to severe depression than among those suffering from slight depression. However, there is no study investigating the relative efficacy of TCAs and SSRIs among these patients. Among the new antidepressants, only the most noradrenergic, such as venlafaxine and reboxetine present an increase in efficacy, especially when compared to SSRIs. Even the increase in the number of suicides during the 15 first days of treatment that was the focus of the media attention is insufficiently supported among the authors. Although there is indeed an increase in suicidal ide-

ations, the TCAs and SSRIs rates are equivalent, and are not associated with an increase of suicidal behaviour. Finally, although side-effects are more frequent with SSRIs than with TCAs, they are not quantitatively comparable in light of their qualitative differences. One will nevertheless notice that the meta analysis of Gualana et al (19) which compared amitriptyline with -- among others -- SSRIs, indicates that amitriptyline is as efficient as SSRIs, the latter led to significantly less side-effects.

Anderson (20) compared SNRI's (serotonin-noradrenaline reuptake inhibitors) and SSRI in a meta-analysis. In addition, this study not only compared SSRI with SNRI, but the author also pointed at differences among SSRIs. Thus, fluoxetine is the least tolerated substance and sertraline is the most tolerated one. Moreover, the increase in efficacy of SNRIs had already been suggested by Anderson in a previous meta-analysis in 1998 (21). In this study that included 25 double-blind studies, the author shows that TCAs present an advantage over SSRIs only when the selected TCAs have an effect on serotonin and noradrenalin receptors, such as amitriptyline, and clomipramine (size of the effect = -0.30; 95% CI -0.54 to -0.05; P = 0.1017). These findings help explain why, in an older frequently cited study (22), clomipramine appeared more effective than paroxetine, citalopram and moclobemide. Following these findings, it is easy to conclude that SNRIs are more efficient than SSRIs, and this explanation might be at the origin of the good results of venlafaxine found in the cost-effectiveness study of by Doyle et al (23). This study was a meta-analysis of international results from 10 countries over a period of 6 months on three types of drugs: venlafaxine, TCAs, and SSRIs. One should note, however, that the notion of "success" in this study was rather generously defined - a 50% symptom reduction compared to the patient's initial score on Hamilton Depression Scale or on Montgomery and Asberg Depression Rating Scale (MADRS). In this study, venlafaxine, prescribed as a first choice, proved to be the most cost-effective. Dardenne et al. (24) have shown similar results with milnacipran - another SNRI. These results confirm the findings of Griffith et al (25) showing that, from a pharmaceutical-economic point of view, the transition to an SNRI after a failure with an SSRI (after at least two months of treatment) is as "cheap" as the transition to a TCA. This multicenter study, which lasted one year and comprised 188 patients under venlafaxine and 172 patients under TCAs, compared direct and indirect medical costs. Nevertheless, the superiority of noradrenergics did not remain undisputed. For example, in his

meta-analysis on more than 15000 patients, Nelson (26) did not observe it.

ANXIOLYTICS

The number of publications comparing molecules in the treatment of anxiety disorders is markedly more limited than for the two categories of drugs discussed above, and inter-class comparisons are of course even more scarce. Although some studies suggest that SSRIs, SNRIs and several TCAs show some efficacy (27) among acute patients, the majority of physicians prescribe benzodiazepines (BZD). Based on our review of the literature, no one has yet compared any of these molecules to BZD. While the preference for BZDs is of course influenced by the "Bobon-Ansseaux" stars, there are no comparative studies assessing the cost-effectiveness of the different BZDs. Because of the side-effects of BZD's such as addiction, dependence, and rebound effect, the guidelines recommend that chronic patients be prescribed SSRIs or SNRIs. However, there are no studies comparing the cost-effectiveness of these different types of treatment with other drugs (SSRI-SNRI-buspirone- β -blockers-neuroleptics, etc.). Most studies, and particularly the study of Baldwin et al (28), compare efficacy between paroxetine and escitalopram. In addition, although this study comprised 600 patients, its duration lasted only 12 weeks. Both molecules were found superior to placebo, and escitalopram proved to be more efficient than paroxetine. One review (29) and one prospective study (30) compared SSRIs with TCAs. While the review concludes that these molecules are equally efficient, the prospective study, conducted with hundred ambulatory psychiatric patients, affirmed the superiority of TCAs. An older study (31) has compared clomipramine, paroxetine and placebo in the treatment of panic attacks over a period of 12 weeks and concluded that clomipramine and paroxetine are equally efficient.

DISCUSSION AND CONCLUSIONS

As can be derived from the literature, there is an important gap between demonstrating the efficacy of a given molecule against placebo in any of these three types of disorders and treatments, and the research data obtained in ambulatory populations. Between these two extremes comparative studies on more than two molecules are emerging. It is however quite unfortunate

that studies comparing cost-effectiveness are so scarce. The frequency of this kind of studies is very different from one topic to another and is more frequent for neuroleptics, less for antidepressants and rare for anxiolytics.

Currently, the main pharmacological strategy consists in first, administering a molecule "x," which is less efficient and presents less side-effects, and when it fails, prescribing another molecule "y," which is more efficient but which presents more side-effects. In light of this review, one cannot help but wonder about the wisdom of such a strategy for the treatment of depression and psychotic disorders. It would make more sense to start with molecule "y" and then move on to molecule "x." This strategy seems to be the most common one in the treatment of anxiety disorders. Typically, it consists in first prescribing benzodiazepines (more efficient but more noticeable side-effects), and then replace them by SSRIs (less efficient but less side-effects). At a minimum, we have to find an optimal balance between side-effects and efficacy. By insisting too much on molecules which are free of side effects, we end up with less efficient products that physicians discontinue recommending, and that patients discontinue taking.

REFERENCES

1. Anonymous. Place des antidépresseurs dans la prise en charge de la dépression en 1ère ligne chez l'adulte. *Folia Pharmacotherapeutica* 2006.
2. Isacsson GRC. Antidepressant drug use and suicide prevention. *International review of psychiatry* 2005; 17: 153-62.
3. Lieberman JA, McEvoy JP, Swartz MS, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353: 1209-23.
4. Jones P, Davies L, Dunn G, et al. Randomized controlled trial of the effect on quality of life of second vs first generation antipsychotic drugs in schizophrenia. *Arch Gen Psychiatry* 2006; 63: 1079-87.
5. Peuskens J, Thibaut F. Treatment of cognitive dysfunction in schizophrenia. *Clin Ther* 2005; 27: 25-37.
6. Stroup S, McEvoy J, Swartz M, et al. Effectiveness of Olanzapine, Quetiapine, risperidone and Ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 2006; 163: 611-22.
7. McEvoy J, Stroup S, Davis S, et al. Effectiveness of Clozapine versus Olanzapine, Quetiapine, and Risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163: 611-22.
8. Citrome L. Schizophrenia, clinical antipsychotic trials of intervention effectiveness and number needed to treat: how can CATIE inform clinician? *Int J of Clinical Practice* 2006; 8: 993-40.
9. Breier A, Thakore J, Naber D, et al. Olanzapine versus ziprasidone: results of a 28 week double-blind in patients with schizophrenia. *Am J Psychiatry* 2005; 162: 1879-87.

10. Csernansky J, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002; 3: 16-22.
11. Leucht S, Kissling W, Engel R, Corell C, Kane J. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003; 7: 1209-22.
12. Liu-Seifert H, Kinon B. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analyses of four atypical antipsychotic drugs. *BMC Medicine* 2005; 3: 1-10.
13. Naber D, Klimke A, Vorbach E, et al. Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatrica Scandinavica* 2005; 111: 106-17.
14. Day JC, Roberts C, Randall F, et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. *Arch Gen Psychiatry* 2005; 62: 717-24.
15. Peveler R, Buxton M, Longworth L, et al. A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine. *Health Technol Assess* 2005; 9: 100-34.
16. Arroll B, Ogston S, Reid I, Sullivan F, Williams B, Crombie I. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med* 2005; 3: 449-56.
17. Steffens DC, Helms MJ. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress Anxiety* 1997; 6: 10-8.
18. Butler R, Cipriani A, Geddes J, Hatcher S, Price J. Depressive disorders. *Clin Evid* 2005; 15: 316-68.
19. Gualana G, Hotopf M. Amitriptyline versus other types of pharmacotherapy for depression. *Cochrane Database Syst Rev* 2003; 2: CD004186.
20. Anderson I. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001; 57: 161-78.
21. Anderson I. SSRI versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; 7: 11-7.
22. Vestergaard P, Kragh-Sørensen P, Bech P, Reisby N, Bolwig TG. Therapeutic potentials of recently introduced antidepressants. Danish University Antidepressant Group. *Psychopharmacology series* 1993; 10: 190-8.
23. Doyle JJ, Arikian S, Tarride JE, Gonzalez MA, Casciano R. A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. *Value Health* 2001; 4: 16-31.
24. Dardennes R, Lafuma A, Fagnani F. Comparison of the cost-effectiveness of milnacipran (a SNRI) with TCAs and SSRIs: a modeling approach. *Eur Psychiatry* 1999; 14: 152-62.
25. Griffiths RI, Frank RG, Strauss MJ, Herbert RJ, Clouse J, Goldman HH. Medical resource use and cost of venlafaxine or tricyclic antidepressant therapy. Following selective serotonin reuptake inhibitor therapy for depression. *Pharmacoeconomics* 1999; 15: 495-505.
26. Nelson JC. A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression. *Biol Psychiatry* 1999; 46(9): 1301-8.
27. Stevens JC. Benzodiazepines in clinical practice: consideration of their long-term use and alternative agents. *J Clin Psychiatry* 2005; 66: 21-7.
28. Baldwin D, Maehlum E. Escitalopram and paroxetine compared to placebo in generalised anxiety disorder. *Eur Neuropsychopharmacol* 2004; 14: 311-2.
29. Zohar J. Anxiety disorders: a review of tricyclic antidepressants and selective serotonin reuptake inhibitors. *Acta Psychiatr Scand* 2000; 403: 39-49.
30. Faravelli C, Ciampelli M, Scarpato MA, Spiti R, Ricca V. A self-controlled, naturalistic study of selective serotonin reuptake inhibitors versus tricyclic antidepressants. *Psychother Psychosom* 2003; 72: 95-101.
31. Lecrubier Y. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatrica Scand* 1997; 95: 153-60.