PROJECT DESCRIPTION

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Project Title
How Effective are Antidepressants?

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Content

Project idea

The current controversy surrounding the antidepressant treatment

Depression is one of the most common reasons for sick leave in Sweden, and both national and international epidemiological studies confirm that this condition is one of the most common causes of Ill-health. From a public health perspective it is therefore urgent that consensus is prevailing regarding the usefulness of different types of antidepressant treatment. What applies to the value of what has for a long time been seen as first-choice treatment, i.e., antidepressant medication of the type selective serotonin reuptake inhibitors (SSRIs), there is for the moment, however, a very worrying lack of consensus.

On one side, about 7% of the Swedish population is for the time being using an antidepressant medication, usually a SSRIs, and those who at any time have been treated with these medications are even far more. And even if these drugs are also used for other conditions there are reasons to believe that the majority of their prescription is for depression treatment.

On the other hand, it has in recent years been suggested that SSRIs in actual fact are lacking antidepressant properties. For example, Irving Kirsch, a professor of psychology at Harvard, has argued that the difference in effect between SSRIs and placebo is too small to be clinically meaningful, and that the difference sometimes noted probably is secondary to the side effects of the drugs; the idea is that the patient who participates in a placebo-controlled study and experience side-effects realizes that he/she has not been chosen to the placebo group and by this experience an enhanced, non-specific placebo effect (1).

Kirsch's questioning of SSRIs have received large media impact; for example, the issue have got significant space in the famous American television program *60 minutes* (2) and been the subject for a 5-page feature article in *Newsweek*. Marcia Angell, who previously was Chief Editor for the medical area's highest-rated journal, *New England Journal of Medicine*, has in the *New York Review of Books* subscribed to the viewpoint of Kirsch (3).

Also in Scandinavia the distrust against antidepressants has had great impact. For example, Peter Gøtzsche, Professor at Rigshopitalet and head of the Danish Cochrane Institute, has in the newspaper *Politiken* stated that we "would be far better off if we removed all the psychotropic drugs from the market" (4).

And in a column in the [Swedish] newspaper *Dagens Nyheter* psychiatry was recently described as "the branch of a cheats and swindlers", with Kirsch's disclosure of the lack of effect of SSRIs as the central argument (5).

Even the [Swedish] National Board of Health and Welfare has been influenced by the questioning of antidepressants. In the last issued guidelines it is true that it is said that they work, but at the same time it is noted that they in the treatment of moderate depression are not more effective (and less cost-effective) than internet-based CBT, despite that this as yet is a method of treatment with very modest support from controlled studies (11). And in line with this approach representatives for British *National Institute for Health and Care Excellence* have claimed that SSRIs in moderate depression probably are not useful at all (2).

In addition to the questioning of the effectiveness of SSRIs, it has also been suggested that they may increase the risk of suicide among patients that before treatment had no suicidal tendencies (6). This hypothesis has influenced clinical practice so that the authorities in many countries (including Sweden) has issued a particular warning for prescribing these medications to children and young people (7), but many believe that this is also a tangible risk when adults take these medications.

The current lack of consensus in this area is deeply problematic. Depression is not only a very common disease, which causes great suffering, and that through sick leave constitutes a considerable burden on society, but also – through the link to increased suicide risk – a potentially life-threatening condition. If it is true that SSRIs do not have specific antidepressant properties, the extensive use of them should stop. But if the questioning is unsubstantiated, on the other hand, the wide spread notion that they are ineffective can lead doctors to refrain from prescribing them and patients to refrain from following a potentially life-saving prescription.

Also if it would be possible to establish that the medication actually exerts antidepressant effect it is also important to clarify *how* they should be used. An important issue is for example, if there are subgroups of depressed patients, definable for example by such factors as age and sex, or by the severity and symptoms profile, where the chance of treatment success is calling, and if it on the other side are groups for which SSRI-treatment is particularly suited. And it is also important to clarify what doses of these drugs are optimal so that they are not regularly under- or overdosed.

Meta-analyses

The execution of clinical trials that could be done to throw new light over the effectiveness of antidepressant medicines, and which would be able to determine for which patient populations they possibly are the most and least suitable, would cost many hundred million SEK to do, and thus is not possible to do for independent university researchers. And it can also, unfortunately, be ruled out that the pharmaceutical industry is going to do new studies in the SSRI area: for all these drugs the patent protection has expired and the commercial value of the drugs is therewith insignificant.

The current questioning of the effectiveness of the SSRIs is based, therefore, not on new studies with negative results, but on analyses of the many placebo-controlled studies that pharmaceutical companies once did to get their drugs approved for marketing. And in that regard one has identified that the SSRIs tested in over 50% of the cases have not shown to be significantly better than placebo (1). In addition, one has with reference to so called meta-analyses, which put together results from both positive and negative studies, argued that the small benefit that despite everything can be noted for SSRIs is too modest to be clinically relevant.

Against this, on the other hand, it can be said that there are for all SSRIs at least two studies in which they actually proved more effective than placebo, which is the requirement for approval, and that the statistical significance of these studies usually is too strong for it to be likely that the outcome will have come from coincidence. A not unreasonable assumption is with this that it for the completed studies exist methodological problems with the effect that one sometimes detects an antidepressant effect and sometimes not.

The current project (I): post-hoc analyses of controlled studies

Since it therefore can be ruled out that someone is going to have the resources to solve the ongoing controversy surrounding the effectiveness of SSRIs through new clinical trials, post-hoc analyses of already completed studies are likely the only passable road in order to clarify whether these drugs work at all. So far conducted meta-analyses (1) may, however, be challenged, inter alia, in that way that they emanate from the average values of the treatment groups in the studies, which makes an analysis of individual predictors of response impossible. In addition, these studies are based on a conventional but strongly questioned endpoint, i.e. the total score of a multifactorial rating scale from the 50's, Hamilton Depression Rating Scale (HDRS) (9).

In order to be able to perform a more advanced and accurate analysis we have asked for *individual-based* data (including information on individual symptoms) from all the studies that have been carried out for the SSRIs sertraline, paroxetine and citalopram, relating to the treatment of depression in adults. Traditionally, companies have been reluctant to release this type of information to independent researchers, but after three years of argumentation we have now access to a comprehensive database covering almost 7000 individuals. We will in short even have access to the corresponding data for the drugs escitalopram and duloxetine, as well as to data from studies on children and adolescents.

We have reasons to believe that this unique database will allow the filling of a series of important questions that have so far been poorly investigated and/or are the subject of controversy. One already published result is for example that we, if we use the traditional effect parameter, i.e. total points on the HDRS-scale, can note a significant difference between SSRIs and placebo in only 44% of the comparisons, but if we, on the other hand, instead use the symptom *depressed mood* as outcome measure, see a significant advantage for the SSRIs in 91% of the studies (10). The often quoted information that one in many of the SSRI studies is not able to detect an antidepressant [effect] is thus shown to be a consequence of the HDRS-scale's built-in problems; if one is using a more sensitive endpoint the antidepressant effect appear on the contrary to be significantly consistent between studies.

In ongoing analyses we have also addressed the question of the relationship between dose and effect, where the usual notion up to now has been that low doses of SSRI is as effective (or ineffective) as higher doses, but where we can demonstrate that this is not true, and that the inclusion of patients treated with a suboptimal dose in the previous meta-analyses by this led to an underestimation of the effect.

In future analyses we intend to analyze if the propensity to respond or not respond to SSRI treatment is associated with for example age, gender, symptom profile or the severity of the disease. Further we will we be able to shed light on the above-mentioned hypothesis that the favorable effect of SSRIs is secondary to patient experiences of side effects and with this only represents an enhanced placebo effect; preliminary results speak against this hypothesis. We will also be analyzing the possible suicide provoking effect of these drugs, as well as how common it is that they give other undesirable effects.

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The current project (II): SSRI prescription in Sweden

During the last few decades a number of factors has led to a drastic increase in the use of antidepressant drugs in Sweden: 1) the introduction of the, from the viewpoint of adverse events, relatively well tolerated SSRI drugs, 2) the decision that depression and anxiety preferably is to be treated in primary care, 3) the intensive promotion of new antidepressant drugs, 4) the discovery that these give beneficial effect also for an array of conditions, in addition to depression, and 5) the increasing destigmatization of conditions like depression and fatigue. But in later years can, as said, to these factors be added new tendencies, such as the growing skepticism toward these drugs as discussed above, as well as an increased enthusiasm for alternative treatment methods (as for example CBT). There are indications that the increased prescription rates have had favorable consequences, so for example the number of suicides has dropped. But on the other side sick leave for depression is still high.

Against the background of the comprehensive prescription of SSRIs it is unfortunate that so little is known about *how* these drugs are handled. Also the link between SSRI prescription and sick leave for depression and fatigue is insufficiently studied.

While earlier discussed analyses, as said, are to be based on data from placebo-controlled SSRI studies, we will with the help of the Prescribed Drug Register analyze the current use of these drugs in Sweden. How many interrupts the treatment shortly after starting, how many takes the medication during the time that traditionally is considered to be required for the treatment of an episodic depression, and how many takes the medication continuously for years? A question of particular interest is also if commonly prescribed doses are consistent with what that has emerged from our own studies (and those of others) regarding optimal dosage, but also such things as choice of drug and the combination of different drugs deserve to be highlighted in a more thorough way than what has been done so far. The extent of the use of SSRIs in individuals who are on sick leave for depression and similar conditions should also be possible to illuminate through the coordination of the Prescribed Drug Register with the register from the Social Insurance Agency.

Relevance

We are alone in the world to have access to a data base with individualised information from all studies about the effect of three (and soon four) of the most used SSRIs in the treatment of depression in adults, and we are about to expand this to also include studies on children and adolescents, studies in which different types of antidepressant medications have been compared, studies about other indications than depression etc. We think with this that the chances are good that our studies will be able to influence the view of antidepressant treatment both in Sweden and internationally. In support of this assumption it can be mentioned that the first report generated by this project has been published in the highest ranked of the psychiatric journals (Molecular Psychiatry; impact factor = 15) (10) and attracted significant international attention both in the specialized press (for example, the British Medical Journal) and other media (for example, The Guardian). In the national perspective will our studies on SSRI prescription rates, based, inter alia, on the Prescribed Drug Register, provide increased knowledge about the effectiveness of the current handling of these drugs. Through to coordination of the Prescribed Drug Register with the register from the Social Insurance Agency we will be able to highlight the presence of SSRI treatment in those who are on sick leave for depression or fatigue.

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Execution

The project has already started and will be executed in the years 2016-2018. The analyses are carried out at the Division for Pharmacology at the University of Gothenburg.

Ethical considerations

Anonymized data are used for all data management. All analyses are approved by the Regional Ethical Review Board or will to be subject to its assessment.

Expected results

The project has already generated results that have brought significant interest in the outside world, and as to part (sic) already has answered one of the central questions we wanted to address, namely if SSRI drugs have any antidepressant effect at all. Our above mentioned observation that one, if one is using a more sensitive endpoint than the conventional, can detect an antidepressant signal in > 90% of all the comparisons that have been made, thus belies that these drugs would be ineffective.

However, a large number of questions remain to highlight, as for example, if it is possible to identify subgroups of patients where the chance that SSRIs exert effect is unusually small and where other methods of treatment, therefore, is to prefer. In addition, we will be able to increase the knowledge about for example optimal dosage, the relative effectiveness of different types of drugs and the risk for increased suicidality during SSRI treatment. The results in these respects are not to predict but it seems likely that we, regardless of their outcome, will generate knowledge that can come to affect future treatment recommendations.

There are several factors speaking for our good opportunities in this respect, among other things, that we have a database that should be unique in its scope, as well as the fact that we, with our identification of a more sensitive endpoint than what previously have been used, have other chances than one previously have had to analyze the actual value of various drugs and doses.

From a national perspective we think that our mapping of the actual use of SSRIs in Sweden will be able to demonstrate the existence of a significant scope for improvement. As a support for this assumption, it can for example be mentioned that the guidelines for depression treatment as issued by the regional pharmaceutical committees not rarely hold dosage recommendations partly contrary to the preliminary results from our post-hoc analysis of controlled studies.

Collaborations

This project is from a group in the pharmacological section at the University of Gothenburg with a large own experience of pharmaceutical studies. We have carried out around ten controlled treatment studies in the psychiatric area, and was for example, the first to show that the condition Premenstrual Dysphoric Disorder responds to treatment with SSRIs, which has led to these drugs now being seen as first-choice treatment for this condition in many countries (including Sweden). For the analyses that are to be based on the Prescribed Drug Register we have established cooperation with Professor Susanna Wallerstedt who has long pharmaceutical epidemiological experience and who previously analyzed aspects of SSRI use in the population. All analyses are carried out in close cooperation with statistical expertise in the form of University Lecturer Staffan Nilsson at Chalmers.

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Utilization, dissemination, communication plan

As already happened (see above) the results will be presented in leading international journals. As a further indication of that they will get good international dissemination it can be mentioned that we already, in spite of the fact that the project is itself in an initial stage, has been invited to a number of international congresses where we have been able to present our results within the framework of seminars or debates. At a national level we intend, as a complement to the publication in international journals, to write a summarized analysis of our results in the Journal of the Swedish Medical Association and likely (given the significant media interest for the question) also in daily newspapers (such as Dagens Nyheter). A PhD student, Frederick Hieronymus, is also connected to the ongoing work within the National Board of Health and Welfare with the purpose to write new guidelines for the treatment of depression.

Literature references

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