St.John`s Wort-

Abstract:

Besides St John's Wort there is little good research supporting the value of other herbs in the treatment of depression. There is some work, for example on crocus [1, 2], but it is very limited and there currently seems no good evidence-based reason to recommend any other herbal preparation besides St John's Wort for depression treatment. In contrast, the literature on St John's Wort is confusing, not because of lack, but because of its quantity and its mixed conclusions. The most recent major Cochrane review of St John's Wort's effectiveness in treating depression[3] was updated in February 2005. It covers 37 rigorously selected randomized controlled trials - 26 include comparisons with placebo and 14 include comparisons with standard synthetic antidepressants.

There were half a dozen earlier systematic reviews published between 1995 and 2000 [3]. In general these reviews painted a rather positive picture of St John's Wort suggesting it was more effective than placebo, as effective as synthetic antidepressants (at least for mild to moderate depression), and better tolerated than synthetic antidepressants in the treatment of adult depression. A recent systematic review of large-scale observational studies also suggests worthwhile benefit and few side effects from St John's Wort treatment of mild to moderate depressive disorder [4]. The National Institute for Clinical Excellence (NICE) guideline on depression treatment – see www.nice.org.uk – was published at the end of 2004 based on

literature searches that were updated over most of 2003. This guideline included a systematic review of St John's Wort research and recommendations about its use that are discussed further below. The Cochrane review is slightly more recent than the NICE guideline as it covers research published up till April/May of 2004. Since then several other interesting studies have come out [5-8] including a further systematic review [9].

The effectiveness of St John's Wort

The Cochrane review acknowledged several major criticisms of St John's Wort's value in more recently published research – both suggesting that, with some forms of depression, it might be no more effective than placebo [10-12] and that it's interactions with other widely used standard medications could be a very real source of harm [13-15]. However, when all good research results were combined, the review concluded that overall St John's Wort appears as effective as standard antidepressants and is associated with lower drop out rates due to adverse effects. In a similar vein, the NICE guideline found very little difference between the effectiveness of St John's Wort and standard antidepressants. In fact the NICE review concluded (p.230) that "In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John's Wort over antidepressants on achieving the likelihood of a 50% reduction in depression symptoms ... ", and even the NICE review's proposition that standard antidepressants may sometimes be more effective than St John's Wort for severe depression is highly qualified as it makes this statement in relation to low dose (not standard or high dose) tricyclics (not SSRI's) – an observation which is largely irrelevant to standard medical treatment of depression. The 2004 NICE guideline "Depression: management of depression in primary and secondary care" is probably the key source of evidence-based advice on how UK doctors should currently treat depression. The guideline's comments on St John's Wort are challenging and to some extent puzzling. In their clinical summary (p. 231) the herb is acknowledged to be "... more effective than placebo on achieving response in both moderate and severe depression ... ". Further commendation comes with the conclusion that "There appears to be no difference between St John's Wort and other antidepressants, other than in moderate depression where it is better at achieving response ... " and the encouraging finding that "... St John's Wort appears as acceptable as placebo, and more acceptable than antidepressants, particularly TCAs (tricyclic antidepressants), with fewer people leaving treatment early due to side-effects and reporting adverse events."

The problem with the research

One might understandably conclude that St John's Wort is now going to be recommended over synthetic antidepressants as the preferred first line treatment for depression. Far from it – the guideline (p. 234) states "... healthcare professionals should not prescribe or advise its use by patients because of uncertainty about appropriate doses, variation in the nature of preparations and potential serious interactions with other drugs ... ". At least they have the honesty to acknowledge this recommendation as only level "C" – just supported by "level IV" evidence – the lowest evidence grade cited by the guideline (p.46). Level IV evidence is based on "... expert committee reports or opinions and/or clinical experiences of respected authorities." In other words there is no level I evidence (randomized controlled trials or meta-analyses), level II evidence (well conducted non-randomized trials), or even level III evidence (well designed descriptive work such as comparative, correlation and case studies) to back up the guideline's recommendations on St John's Wort. St John's Wort is a newcomer on the block as far as the medical establishment is concerned. To be blunt, doctors have been wined and dined by the drug industry for far too long. We know from level I evidence (p.179 of the guideline) that "Most studies of the effects of drugs are sponsored by the drug industry, and these have been shown to be more than 4 times as likely to demonstrate positive effects of the sponsor's drug as independent studies.[16]" There has been a blizzard of further solid reports and research studies showing that bias is a huge problem in the drug literature [17-21]. Level I evidence meta-analysis even throws serious doubts on just how effective synthetic antidepressants really are [22]. If the medical establishment is going to make an evidence-based statement that keeps the outsider St John's Wort from 'joining the party', it seems to me that we need better data for taking that recommendation particularly seriously than level IV "opinions and/or clinical experiences of respected authorities." As has frequently been noted "The plural of anecdote is not data".

When might one use St John's Wort?

To give the NICE guideline its due, it notes (p.8) that "Guidelines are not a substitute for professional knowledge and clinical judgement". So when might one consider using St John's Wort for depression? I can see several possible reasons why an informed practitioner or person affected by depression might well think seriously about this option. These include:

- 1. Negative attitudes to synthetic antidepressants. A large scale survey [23] of general public attitudes to depression in the UK published in 1996 found that 85% "believed counselling to be effective but were against antidepressants" with 78% "regarding antidepressants as addictive." More recent publicity on the increased suicidal thoughts many people may face early in treatment, problems with side-effects during treatment, and difficulties when trying to come off these medications, combines with the stigma many people feel taking these drugs to produce very understandable problems with acceptance and compliance. This may well mean that many people who would benefit from treatment, are not prepared to accept the offer of a synthetic antidepressant. Clinical experience suggests that quite a high proportion of these people would be prepared to try St John's Wort. It would be fascinating to check this impression in a clinical trial.
- 2. A preferable side-effect profile. Meta-analysis has repeatedly shown that St John's

Wort is better tolerated than synthetic antidepressants. Besides the probems already mentioned, synthetic antidepressants are often plagued by their aggravation of sexual difficulties [24, 25] weight gain [26], nausea, diarrhoea, headache and other problematic effects including, of course, the danger of fatal overdose [27]. The most commonly reported side-effects with St John's Wort are gastrointestinal symptoms such as nausea, dermatological symptoms such as itching and increased light sensitivity, and occasionally fatigue, sleep disorders, and headache. It is well worth noting though that, in randomized controlled trials, St John's Wort only produces side-effect rates that are similar to those produced by inactive placebos [28].

- 3. Increased effectiveness with certain types of depression. Much more research is needed here, but there is preliminary data suggesting St John's Wort may be a good treatment choice with atypical symptoms such as increased appetite and increased sleep [29], where there are multiple unexplained physical (somatoform) symptoms [30], in juvenile depression [31], and in agitated depression [32].

Issues to note and side-effects

Key issues to note if someone is taking or considering taking St John's Wort are the potential for drug (and light) interactions, the variability of different types of St John's Wort, and the obvious need to review treatment if, after about four weeks, there is inadequate treatment response. Drug interactions are common with many medications. For example the NICE guideline notes (p.199) that the SSRI's "Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes precipitating many significant drug interactions." In this kind of situation care, but not a blanket veto on use, is needed. To quote a recent authoritative systematic review of adverse effects due to St John's Wort [33] "A wide range of drug interactions has been described in the recent past [34], but the clinical relevance of these interactions is not clear, as many of these interactions as actual side effects in patients have not been observed or reported. The lowering of plasma cyclosporine concentration in transplant patients is obviously of great importance ... Hypericum extracts should also not be used in HIV-infected patients receiving antiretroviral treatment. In patients receiving anticoagulants of the coumarin type, the use of hypericum is only acceptable if coagulation parameters are regularly monitored. Simultaneous use of hypericum extracts and other antidepressants, particularly SSRI's, is inadequate and can be harmful. The question whether hypericum extracts interact with oral contraceptives is of major relevance but has been difficult to answer up to now. A recent randomized trial [35] in a limited number of healthy females taking low-dose oral contraceptives found no evidence of ovulation in subjects taking a hypericum extract, but intracyclic bleeding episodes increased. Patients should be informed that an interaction cannot be ruled out with certainty. Finally hypericum extracts should be avoided in patients with a known allergy or hypersensitivity to such products." The March 2005 edition of the British National Formulary[36] (BNF) gives a longer list of possible problematic interactions between St John's Wort and other medications, including some antiepileptics, digoxin, simvastatin, theophylline, and other drugs. Generally what happens is that St John's Wort lowers blood levels of these agents. It is therefore important, if you are considering taking St John's Wort with any other medication, that you check on the safety of the combination. Strength of interaction is likely also to vary with the brand of St John's Wort [37]. It is well worth

noting though that the list of cautions for St John's Wort is considerably shorter than the list of possible drug interactions given by the BNF for SSRI antidepressants, for tricyclic antidepressants or even for antihistamines. The sensible and very informed Knuppel and Linde review went on to report research showing that available St John's Wort preparations can vary considerably in quality and even batch to batch composition [38-40]. The authors suggest that ideally one should use products that have been tested in clinical trials – the most widely researched is the Kira brand produced by Jarsin and quite easily available in the UK. They go on to suggest that one should avoid products that do not give important content information such as the amount of total extract, the extraction fluid, and the raw material to extract ratio. One economic option would be for an individual to start with the relatively expensive Kira brand and, if there is an adequate response, then later see whether a reputable but cheaper alternative product is as effective.

Conclusion

I will leave the final coment on St John's Wort to Klaus Linde whose meta-analysis[41] has been so helpful in clarifying the value of this herb: "In conclusion, the available evidence suggests that hypericum extracts are well tolerated and safe if taken under the control of a physician who is aware of potential risks in specific circumstances. Self-medication might be acceptable in patients who have very mild depressive symptoms and who are not taking any other medication."[42]

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