

Case study

Hypomania induced by herbal and pharmaceutical psychotropic medicines following mild traumatic brain injury

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The use of herbal medicines has become a very common practice. While many are safe enough to be available over-the-counter, they may pose risks due to interactions with pharmaceutical medications and effects in specific clinical populations. The case of a female patient with a history of mild traumatic brain injury and resulting depression is presented. She experienced hypomania after adding St John's wort and Ginkgo biloba to her regimen of fluoxetine and buspirone, which remitted after discontinuation of the herbal medicines. Implications for interactions between various psychopharmacologic agents, including herbal medicines and selective serotonin reuptake inhibitors (SSRIs), as well as the need for appropriate patient and health care provider education are discussed.

Introduction

Herbal medications have become increasingly popular in the last decade, amounting to a multi-billion dollar industry in the US [1]. It has been extrapolated that over 40% of people in the US have used at least one form of complementary and alternative medicine (CAM), including herbal medicine. This is especially relevant to treatment of mental illnesses, since over half of Americans experiencing anxiety or depression report using CAM, either alone or in conjunction with standard therapies [2]. People also sometimes resort to CAM to treat neurological disorders: 24% of a sample of patients seen in an epilepsy clinic reported consulting use of CAM [3]. Herbs and supplements were the most commonly used form of CAM among this sample.

There are many possibilities for pharmacological interactions between herbal medicines and standard pharmaceutical medications [4]. This fact, coupled with a tendency by many patients to not inform their physicians of their use of CAM therapies, creates a potential for unintentional side effects [1, 3]. It has been estimated that 15 million adults took herbal medications and/or high doses of vitamin supplements concurrently with prescription medications in 1997 [1].

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St John's wort

St John's wort (*Hypericum perforatum*) is a flowering perennial plant that has gained a reputation for having antidepressant effects. Meta-analyses have supported this, suggesting that St John's wort is superior to placebo for treatment of depression of mild-to-moderate severity [5–7]. However, one recent study has challenged these large-scale analyses [8]. St John's wort has been shown to be equivalent to several pharmaceutical antidepressants, including fluoxetine and sertraline [9–12]. The exact mechanism of the putative antidepressant effects of St John's wort is not known; however, a combination of actions that increase monoamine activity is likely [13–17]. Animal models and human electrophysiological data further support a central effect of St John's wort [18–25]. Similarly to the pharmaceutical antidepressants, there is a 10–14 day lag for the onset of the therapeutic effects of St John's wort [26, 27].

A few cases of adverse reactions to St John's wort have been reported relevant to SSRIs and hypomania. One case involved concurrent use of St John's wort with paroxetine, causing transient lethargy, nausea, and weakness, followed by a return to normal status [28]. Two cases of hypomania have been reported resulting use of St John's wort use without any other concurrent psychotropic medications [29]. One such case involved a patient with post-stroke depression and a history of unsuccessful treatment with other antidepressant treatments: paroxetine, fluoxetine and ECT (not concurrent with St John's wort). Manic symptoms subsided after discontinuation of St John's wort and addition of valproate. Other cases have been reported, including one with combined testosterone replacement, sertraline and St John's wort [30]. Some cases of hypomania with St John's wort involve a prior history of bipolar disorder, or similar responses to an SSRI [31, 32].

Ginkgo biloba

Although primarily recognized for its cognitive effects, there is some research which hints that ginkgo has potential mood-altering effects. Animal studies suggest that a ginkgo/ginger combination has anxiolytic effects [33]. Ginkgo alone may reduce learned helplessness and stress-induced memory deficits in animals [34, 35]. One human clinical study suggests that ginkgo may augment the effect of pharmaceutical antidepressants [36]. However, ginkgo extract alone is not effective for treatment of seasonal affective disorder [37].

While ginkgo extract does contain some monoamine oxidase (MAO)-inhibiting constituents, they are not potent enough in oral doses to be significant by themselves [38, 39]. Through an unknown mechanism, chronic treatment with ginkgo extract does alter monoamine receptors: it prevents age-related reductions and stress-induced desensitization of 5-HT_{1A} receptors [40–42]. It also reverses an age-related decline in the binding density of α_2 -adrenergic receptors [43]. Ginkgo constituents reduce the production of glucocorticoids [44–46]. Overactivation of the hypothalamic-pituitary-adrenal axis is associated with anxiety and depression, and there is good theoretical rationale for anti-glucocorticoid drugs in the treatment of depression [47].

Case description

History

D.B. is a 42-year-old right-handed female who was referred for cognitive remediation 17 months after a motor vehicle accident in which she sustained a cerebral concussion. She was the unrestrained driver of a vehicle hit from behind. Her head struck the windshield and she sustained a loss of consciousness for the duration of at least a few seconds. There was no retrograde amnesia, but there was a period of disorientation and altered consciousness for a few hours post-injury. She was evaluated and x-rayed in a local emergency room and discharged in a Philadelphia collar with diagnosis of cervical strain/sprain and concussion. Subsequently, she experienced cognitive and physical difficulties, including deficits in concentration and memory, and pain in her neck and left shoulder for which she received 4 months of intensive physical therapy. Emotional adjustment difficulties arose for which she consulted a psychiatrist 3 months post-injury. She was diagnosed with major depression and prescribed fluoxetine and buspirone, to which she was partially responsive.

Neuropsychological evaluation was performed 10 months post-injury and revealed impairments in information processing speed, sustained and complex auditory attention, working memory, and auditory-verbal learning. Executive dysfunction included deficits in verbal reasoning, poor ideational generation, impulsivity, impaired self-monitoring and diminished organizational/planning skills. Basic attention/concentration, confrontation naming, visuo-perceptual ability, visual learning and memory, non-verbal problem solving and conceptualization were within normal limits.

Social history reflects that D.B. is the divorced mother of a young adult daughter. Past medical history is non-contributory and there is no history of developmental delay or educational deficits. Prior psychiatric history and drug and alcohol use were denied. She is a registered nurse who worked in hospital nursing for many years prior to her injury.

Initial presentation

D.B. initially presented as anxious, with constricted and depressed affect. Speech was clear and fluent, but tangential and disorganized. Her self-description as 'overwhelmed' aptly fit her demeanor. She exhibited symptoms of depression, including excessive self-criticism, hypersomnia, increased appetite, and weight gain. A primary complaint was her inability to manage financial and health care-related tasks, finding them overwhelming. She also reported anxiety that interfered with her functioning. At time of admission for weekly cognitive remediation sessions, her medications included fluoxetine (20 mg bid) and buspirone (15 mg bid).

Two months after the beginning of cognitive remediation, D.B. reported that her buspirone was increased to 20 mg bid due to her persistent anxiety. Not long thereafter, she began missing and coming excessively late to treatment sessions, with reports of over-sleeping and worsening memory deficits interfering with attendance. Over the next few weeks, she appeared increasingly anxious in session, and was non-compliant with homework assignments. She reported a disrupted sleep-wake cycle, characterized by nighttime insomnia. Racing thoughts also began to develop, which manifested behaviourally as agitation and hypervocal, pressured speech.

Inquiry revealed that she had been taking Ginkgo biloba extract, melatonin, and St John's wort extract (in unspecified doses) over the past several weeks in addition to fluoxetine and buspirone.

D.B.'s responses on the Beck Anxiety Inventory reflected a severe degree of symptomatology (BAI=28) [48]. There were moderate somatic manifestations, including tingling, feeling hot, lightheadedness, and trembling hands. Reported subjective and panic-related symptoms included feeling unable to relax, terrified, nervous and scared. The degree of depression was also assessed as severe [49]. Her behavioural presentation and self-reported symptomatology were consistent with a mixed hypomanic episode, with prominent anxious features and underlying depression. At her therapist's insistence (L.E.), she was seen by her psychiatrist the following day, who instructed her to discontinue all non-prescription medications.

Subsequently, the self-report and behavioural manifestations of anxiety diminished. With increased affective stability, her ability to focus on treatment improved. Over the course of an additional 3 months of treatment, she was able to improve her organizational strategies and manage some responsibilities. She continued to experience depressed mood, and it was recommended she participate in psychotherapy to address long-term adjustment to chronic disability. She followed through with this recommendation and was continuing in this form of treatment 6 months later, at last follow-up.

Discussion

This case adds to the small number of cases of hypomania likely induced by a combination of St John's wort extract and a SSRI. The likelihood that the herbal medicines contributed to the induction of hypomania is suggested by the close temporal relationship between the addition of the herbal medicines and the behavioural changes. Also, there had been no prior history of mania or bipolar disorder. The commonality of monoamine mechanisms between SSRIs and St John's wort make this a probable mechanism for potentiation of antidepressant effects, although others are possible. Whether or not St John's wort alone is clinically effective for depression is less relevant in such cases, since a synergistic effect could occur once the drugs are combined.

Buspirone is another potential contributing factor to the development of hypomania in this case. Buspirone itself may have some antidepressant effects, and it augments the effects of SSRIs [50–52]. Several cases have been reported of probable induction of hypomania by buspirone [53–56].

This is also the first such case to also involve ginkgo biloba, which may have contributed to the hypomanic presentation. Oral doses of ginkgo have been shown to have activating effects on the electroencephalogram [57]. Its effects on glucocorticoids and possible augmentation of pharmaceutical antidepressants could contribute to the induction of hypomania [58]. Whether or not it played a role in this case cannot be assessed, since all medications were taken concurrently.

D.B. was also taking melatonin around the time she developed hypomania. Unlike the other medications, melatonin was not likely to contribute mood instability in this case. There are few controlled studies of exogenous melatonin in mania. However, the existing studies do not indicate induction or exacerbation of mania in bipolar patients by oral melatonin [59, 60].

Another possible contributing factor to the development of hypomania in this case is the presence of neurological insult. Other reported cases of mania with SJW have involved cerebrovascular accidents, but this is the first case to involve traumatic brain injury (TBI). TBI is known to produce alterations in mood and greater mood instability [61–63]. It is very possible that the presence of significant TBI, resulting in depression and cognitive disturbances, increased D.B.'s mood lability.

The fact that this patient was a registered nurse also did not prevent her from combining medications, although it is arguable that her judgement may have been subtly affected by the TBI. None the less, cases such as this underscore the potential for pharmacological interactions between pharmaceutical and herbal medications. The vigilance of health care providers in the present case fortunately allowed the problem to be identified and corrected. These problems are not unique to herbal medicines: while herbal medicines are largely unregulated, patients taking other pharmaceutical over-the-counter medications run the same potential risks. There is a need for education of both patients and health care providers regarding the safety and efficacy of herbal medicines. Proactive inquiries and recommendations by informed health care providers remains the best method to avoid unintentional and unnecessary drug interactions.

Conclusions

Evidence for causality/study limitations

This patient represents another case of hypomania induced by combining herbal medications with pharmaceutical antidepressants. However, it appears to be the first reported case of hypomania following brain injury and involving multiple mood-altering herbal and pharmaceutical medications. The temporal relationship between the taking of the medications and the onset of hypomania, as well as the remission of hypomania following discontinuation, strongly suggest that the medications were causal agents. Further, the ability of fluoxetine, buspirone, St John's wort, and possibly ginkgo, to elevate mood has been documented. While the above factors suggest a causal relationship between the concurrent use of herbal and pharmaceutical psychotropic medication and development of hypomania, this case study has several limitations. The doses of the herbal medications were not carefully monitored by the client, which could greatly alter their relative contribution to the clinical picture. By nature, this case study only involves a single subject, so the contribution of multiple other extraneous, non-pharmacological factors cannot be ruled out. Although she had no prior history of bipolar disorder, it is possible that she may have developed this condition in any case. Indeed, the additional presence of a mild TBI may have further predisposed her toward mood lability. The presence of multiple psychotropic medications also precludes one from knowing which combination of medications is sufficient to induce hypomania.

Implications for rehabilitation

A number of recommendations are offered for health care, rehabilitation and mental health providers. First and foremost, clinician training in psychopharmacology must encompass education regarding herbal and over the counter medications and side effects/drug interactions. While such training is now increasingly being integrated

into graduate training programmes, it behooves clinicians who have not had such training to seek appropriate educational on the topic (e.g. conferences and seminars). Rehabilitation therapists from all disciplines will benefit from such knowledge and training. While training in the psychopharmacology of herbal medicines is not commonplace, there are available sources [17].

A number of issues regarding brain injury rehabilitation are also raised by this case. Clients are best served by coordinated patient care, involving routine communication and collaboration between treating clinicians and the prescribing physician. Therapist information regarding formal medication changes allows for feedback to the prescribing doctor and better monitoring of changes in mental status or behaviour which may reflect prescribed drug side effects or signal interaction effects from other non-prescribed medications. This direct therapist-physician communication is particularly important in brain injury rehabilitation, as clients may not be cognitively able to provide accurate information regarding medication changes or dosages, due to attention, memory or other neuropsychological deficits.

Involvement of the client's family and others within the social support system is also important. Appropriate (i.e. consensual) contact and communication with significant others can be helpful in appropriately documenting the brain injured client's medicinal regime, and in the identification of self-medication. In this instance, there was minimal communication with significant others (at the client's request), and she was ultimately unable to specifically indicate the dosages of the various herbal medications that she was ingesting. This communication can also be a source of input regarding more subtle emotional or behavioural changes that may indicate negative drug interactions or self-medication.

The present case also highlights the importance of thorough inquiry in the exploration of possible causes of behavioural and mental status changes. While there may be more benign causes of affective changes following brain injury, such as increased psychosocial stressors, specific questioning regarding issues of self-medication allowed for the identification of this behaviour in this case. In addition, a strong therapeutic relationship will allow for exploration and discussion of client concerns about refractory symptomatology. This may offset the likelihood of self-medicating behaviour, and facilitate the exploration of other therapeutic interventions and healthy, proactive behaviours to address symptomatology.

Lastly, education provided to brain-injured clients and their families should be expanded to include the use of verbal information and written guidelines regarding the use of herbal and over the counter medications. Such information can be easily incorporated within the instructional format typically provided to clients regarding the dangers of illicit drug and alcohol use following brain injury. The education of both patients and health care providers is suggested as the most effective means of avoiding unnecessary and potentially harmful interactions.

Implications for research

This case highlights the need for several forms of research which would address the concerns discussed here. The common and surreptitious use of herbal medicines in both normal and clinical populations indicates an abundant potential for interactions with standard therapies [1-3]. While the prevalence of usage has been investigated in some clinical populations, such as anxiety, depression, and epilepsy, it has not been formally studied in TBI. Such data would be relatively convenient to collect

and would greatly inform one about the extent of this issue. Further, there is both clinical and experimental evidence which indicates that St John's wort and ginkgo may be useful to treat the cognitive and emotional sequelae of TBI. Methodologically-controlled (randomized, placebo-controlled, double blind), prospective studies would be necessary in this respect.

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