

Single treatments that have lasting effects: some thoughts on the antidepressant effects of ketamine and botulinum toxin and the anxiolytic effect of psilocybin

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Recent clinical trials suggest that 3 single biological treatments have effects that persist. Based on research showing that the muscles involved in facial expressions can feed back to influence mood, a single trial diminishing glabella frown lines with botulinum toxin demonstrated a significant antidepressant effect for 16 weeks. Based primarily on research with animal models of depression suggesting that glutamate may be involved in depression, the *N*-methyl-*D*-aspartate antagonist ketamine has been tested in several trials. A single dose decreased depression for up to a week. The reported effects of the use of mushrooms containing psilocybin by a number of cultures around the world has stimulated several trials showing beneficial effects of a single dose of psilocybin for over a year in healthy people, and for up to 3 months in patients with anxiety disorders who have advanced cancer. This article discusses these studies, their rationale, their possible mechanisms of action, the future clinical research required to establish these therapies and the basic research required to optimize single treatments that have lasting effects.

Introduction

Many treatments in psychiatry are not particularly effective and take a while to act. Furthermore, some psychological treatments may have more lasting effects than drug treatments. For example, relapse of depression occurs at a lower rate after cessation of psychotherapy than after cessation of pharmacotherapy.¹ This article discusses 3 biological treatments that are given once and are claimed to have a lasting effect. A single dose of ketamine may improve depression for about a week. The treatment of glabellar frown lines with botulinum toxin was reported in a single study² to have a marked antidepressant effect. In healthy people, psilocybin can cause sustained positive changes in attitudes, mood and behaviour, and a recent study suggests it may be helpful in the treatment of anxiety.³ Of the 3 treatments, the one that may seem unlikely is the use of botulinum toxin to improve depression; however, this is possibly the one with the best rationale based on basic research. The purpose of the present article is to review the work that has been done with the 3 treatments, assess the extent to which their therapeutic action may be attributed to the placebo effect and discuss fur-

ther research that needs to be done. If these treatments are proven to be effective, it could be important for 2 reasons. First, not having to take medication every day may be more acceptable to patients and may improve the currently low adherence levels seen with many biological treatments.⁴ Second, these treatments are novel and may provide insight that results in research on potential biological treatments with a wider range of mechanisms.

Ketamine

The first indication that the *N*-methyl-*D*-aspartate (NMDA) receptor may be a useful target for antidepressant treatment came in 1959 from Crane,⁵ who studied the effects of the anti-tuberculous drug cycloserine on mood in patients with tuberculosis who were also depressed. He concluded "it reverses depressions to normal." Although it was not known at that time, cycloserine is a partial agonist of the glycine site of the NMDA receptor. The idea that glutamate may be involved in the pathophysiology of depression and that compounds that block NMDA function may have an antidepressant action was first formulated by Trullas and Skolnick⁶ in 1990. The

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J Psychiatry Neurosci 2013;38(2):78-83.

Submitted July 5, 2012; Revised Sept. 13, 2012; Accepted Sept. 17, 2012.

DOI: 10.1503/jpn.120128

idea came from experiments using an animal model of depression. A recent review of the experimental evidence supporting a role of glutamate in depression⁷ points to a substantial body of evidence derived from animal models of depression. Clinical data are more limited, given the difficulty of studying glutamate function in the brains of patients.

The first study using the NMDA antagonist ketamine in depressed patients, which was conducted by Berman and colleagues in 2000,⁸ used both the animal models and the study by Crane⁵ as a rationale. Berman and colleagues treated 9 patients with ketamine (0.5 mg/kg infused intravenously over a period of 40 minutes) or placebo administered in a randomized double-blind manner, with the treatments occurring 1 week apart. The subjective effects of the ketamine were finished 2 hours after starting the infusion, but mood, as measured by the Hamilton Rating Scale for Depression (HAM-D), was improved at 6 hours and at 1, 2 and 3 days after treatment. Zarate and colleagues⁹ used a similar design with 18 treatment-resistant patients after a 2-week drug-free period. The subjective effects of the ketamine were finished within 110 minutes of starting the infusion. Ketamine improved mood, as measured by the HAM-D, starting 100 minutes after infusion and continuing for 7 days. Diazgranados and colleagues¹⁰ also used a similar design, except that the 18 treatment-resistant patients were taking lithium or valproate for bipolar disorder, and the interval between ketamine and placebo was 2 weeks. Improvement in mood on ketamine occurred within 40 minutes and remained significant through day 3. The same group replicated these results in a further 15 patients being treated for bipolar depression; they observed a significant decrease in suicidal ideation after ketamine treatment.¹¹ The results from all these controlled trials are consistent with the results of a number of open trials that have been discussed in recent reviews.¹²⁻¹⁴

In humans, the half-life of anesthetic doses of ketamine, which is higher than those used in the study of its antidepressant action, is about 3 hours.¹⁵ Therefore, the antidepressant action of ketamine continues well past the time in which it is entirely eliminated.

Botulinum toxin

The injection of botulinum toxin into a variety of sites in the head and neck is an established prophylactic treatment for migraine.¹⁶ This is one example of a variety of ways in which modulating feedback from the periphery to the brain can influence important aspects of brain function. Another example is the ability of manipulation of pupil size to influence specific aspects of cognitive processing.¹⁷ Even so, the idea that treatment of frown lines with botulinum toxin might improve the mood of depressed patients might seem far-fetched. However, the rationale for this treatment is based on the facial feedback theory, which is a century old. It suggests that when people make facial expressions there is feedback from the muscles in the face that can modulate the subjective experience of emotion.¹⁸ While the original mechanism proposed — that changes in blood flow to the brain are due to the action of facial muscles on the blood vessels — is not cor-

rect, over the past 3 decades research has demonstrated the phenomenon and provided some insight on its mechanism and implications. Ekman and colleagues¹⁹ studied a variety of measures of autonomic nervous system activity in healthy adults when they either relived past emotional experiences or were asked to activate facial muscles, one by one, to create different emotional expressions. There were changes in the pattern of autonomic activity, in response to both forming expressions and reliving past emotional experiences, that were emotion-specific. This study helped to establish that formation of facial expressions could provide emotion-specific feedback to the nervous system.

Strack and colleagues²⁰ studied whether facial feedback could influence perception of emotion. Participants were asked to hold a pen with their lips only, or with the teeth only. The rationale for holding a pen in their lips was that this “would be incompatible with contracting the zygomaticus major or the risorius muscles that are used when smiling,” whereas holding a pen in their teeth “would mainly contract” the same muscles that are part of the smiling response. Participants rated cartoons funnier when holding the pen in their teeth than in their lips. This is consistent with the idea that activation of the muscles associated with smiling would feed back to enhance positive emotions. Larsen and colleagues²¹ extended this approach to a negative expression. To get participants to frown their brows without asking them to do so, they attached 2 golf tees to the participants’ brows, just above the inner corner of each eye. They asked them to touch the tips of the golf tees together, or to hold them apart as still as possible, as part of a divided attention experiment. Touching the tips would involve contracting the corrugator supercilii muscles, which cause brow-furrowing, resulting in a sad facial expression. When viewing sad pictures, the participants felt sadder when causing the tips of the golf tees to touch, indicating that brow-furrowing caused a lowering of mood.

Given that particular facial muscles can alter the perceptions of mood and that brow-furrowing can lower mood, the next pertinent question is whether paralyzing facial muscles can prevent the effects on mood. Several studies have tackled this question and produced results suggesting that botulinum toxin injections may alter emotional responses, as expected.²²⁻²⁴ However, lack of adequate control groups or of clear-cut results makes this conclusion tentative. Hennenlotter and colleagues²⁵ studied participants 2 weeks after botulinum toxin injections into the corrugator muscles, producing complete corrugator paralysis.²⁵ The control group comprised participants who were studied before receiving botulinum toxin injections. Both groups were scanned using functional magnetic resonance imaging (fMRI) before and during a task in which they viewed angry and sad faces, preceded by instructions to either imitate the expression or just observe it. In the group that received botulinum toxin, imitation of sad faces produced activations that were not different from those in controls, but imitation of angry faces attenuated “activation of the left amygdala and its functional coupling with brain stem regions implicated in autonomic manifestations of emotional states.”

These studies provided the rationale for a recent trial by Wollmer and colleagues,² studying the effect of injecting

botulinum toxin into 3 sites in the glabella region of depressed patients ($n = 15$) who were stable on up to 2 antidepressant treatments. The treatment was the same as that used in the cosmetic treatment of frown lines, and the placebo treatment ($n = 15$) was saline injections at the same sites. There was a significant decrease in scores on the 17-item HAM-D, from 2 weeks to the end of the trial (16 wk), on the active treatment relative to placebo. Similar results were seen on the Beck Depression Inventory and the Clinical Global Impressions Scale. At the primary end point, the HAM-D scores at 6 weeks, the mean difference between active and placebo treatments was 10 points, a large effect size.

Psilocybin

Recently, Studerus and colleagues²⁶ reviewed the effect of psilocybin in healthy people. They pointed out that the genus of mushrooms that produces psilocybin occurs throughout the world and has been used in rituals for many centuries. They reviewed studies on psilocybin conducted by their group in the 1960s and '70s, which demonstrated that psilocybin acts for 4–6 hours to produce illusions and hallucinations, although reality testing remains intact, and that it enhances affective responses and the ability for introspection, while activating vivid memories. They pointed out that research on psilocybin became more difficult during the 1970s and '80s owing to widespread nonmedical use, but research resumed in the 1990s. They pooled data from 8 placebo-controlled experimental studies carried out between 1999 and 2008. Of 110 healthy participants who received 1–4 doses of psilocybin, most experienced the “profound changes in mood, perception, thought and self-experience [induced by psilocybin] as pleasurable, enriching and non-threatening.” Negative experiences consisting of dysphoria, anxiety or panic occurred in only a small number of participants receiving the highest doses, and were managed by providing interpersonal support. Ninety of the participants were interviewed briefly between 8 and 16 months after receiving psilocybin. Some changes in behaviour were reported. For example 25% reported a positive change in relationships with others, whereas only 7% reported a negative change.

Griffiths and colleagues performed 2 trials of psilocybin in hallucinogen-naïve healthy people who participated in religious or spiritual practices. The first study²⁷ was designed carefully to minimize any effect due to expectation. Participants were told they would have 2 or 3 sessions occurring 2 months apart. In at least 1 session they would receive a moderate or high dose of psilocybin, while in the other sessions they would receive either placebo or one of various psychoactive drugs (dextromethorphan, nicotine, diphenhydramine, caffeine, methylphenidate, amphetamine, codeine, alprazolam, diazepam, triazolam or secobarbital). In the main part of the study, 30 participants were randomly assigned to receive psilocybin and methylphenidate using a crossover design. Participants were assessed during the treatment, shortly afterwards, and 2 months later. At 2 months, participants “rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience

sustained positive changes in attitudes.” At a further follow-up at 14 months,²⁸ most participants rated their experience with psilocybin among the most personally meaningful and spiritually significant experiences of their lives and felt it had increased their well-being and life satisfaction. These changes were consistent with change scores reported by 3 family members, friends or colleagues of each participant. In the second study, Griffiths and colleagues²⁹ studied 18 healthy participants over a period of 5 sessions during which they received 0, 5, 10, 20 and 30 mg/70 kg body weight of psilocybin. The results were similar to those of the first study. In addition, they found that the lowest dose showed significant effects and that the effects increased as the dose increased. In both studies, participants were administered the NEO Personality Inventory at screening and at 2 and 14 months after treatment with psilocybin.³⁰ Although psilocybin did not change ratings of neuroticism, extraversion, agreeableness or conscientiousness, it increased ratings of openness. The changes in openness were related to scores on a scale that assessed the degree of mystical experience during the psilocybin experience.

Grob and colleagues³ performed a pilot study of the effect of psilocybin on 12 patients with advanced-stage cancer and a diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer or adjustment disorder with anxiety. Using a crossover design, the patients were treated with psilocybin and niacin placebo (to cause flushing) several weeks apart. Psilocybin did not cause any clinically significant adverse effects. It caused a significant decrease in anxiety, as assessed by the State-Trait Anxiety Inventory at 1 and 3 months after treatment, and improved mood, as measured by the Beck Depression Inventory after 6 months.

Discussion

The placebo effect

A valid double-blind trial occurs only when the participants are unaware of whether they received the active treatment or placebo. Although the trial of botulinum toxin² included a placebo treatment, the possibility remains that all or part of the findings were due to a placebo effect. At the end of the study trial, “90% of the participants guessed their group allocation correctly with firm conviction” owing to the cosmetic change or lack of it. Patients were included only if they had “a moderate to severe vertical glabellar line during maximum voluntary frowning,” and presumably patients consented to participate only if they thought the rationale for the treatment was plausible. Therefore, expectation might have influenced the change in mood in those patients who responded. Although the rationale for the treatment, the magnitude of the change and the duration (16 weeks) of the response argue against a placebo effect as the main mechanism of action, further studies are needed in which the placebo treatment produces visible cosmetic enhancements to strengthen the blinding. Suitable placebo treatments would have to be as plausible as injection of botulinum toxin into the glabella region, but would have no theoretical rationale as a treatment for depression. A possibility would be botulinum toxin treatment of

lines in the face that do not contribute to negative expressions, or injection of a filler into the glabella region to reduce wrinkles without affecting muscles, as used in 1 experimental study.²⁴ The important issue is not whether the patients would be able to distinguish between treatments, but whether they would have similar expectations of the 2 treatments. Obviously, expectations would have to be measured to ensure that they were similar for the 2 treatments.

As discussed previously, Griffiths and colleagues²⁷ used an elaborate placebo-controlled design to try and eliminate any effect of expectancy during the administration of psilocybin. However, the researchers who were present with the participants during their psilocybin and methylphenidate sessions were able to guess the treatment correctly more than 70% of the time. Nonetheless, whatever role expectation or placebo may have had in short-term changes, the fact that the participants' view of the world and behaviour, as assessed by others, was changed 14 months after the psilocybin experience suggests that the placebo effect played little or no role in longer-term effects.

Although the ketamine studies described previously were placebo-controlled, no assessment of the adequacy of the blinding was completed. The changes in the subjective experience of the patients during ketamine infusion were measured and shown to be significantly greater than with placebo. Thus, most patients almost certainly knew when they were getting ketamine versus placebo. Given that the antidepressant effect of ketamine lasted only a matter of days, this raises the question of what role expectancy and the placebo effect might have played in mood changes. This problem could potentially be overcome by the use of an active placebo treatment: a drug that causes a clinically important subjective experience, like ketamine.

If a drug that blocks NMDA receptors has an antidepressant effect without the dissociative effects of ketamine, that would support the idea that the effect of ketamine is not related to expectation. Memantine is a noncompetitive antagonist with low to moderate affinity for the NMDA receptor that has no dissociative effects. Memantine, given orally for 8 weeks, was not better than placebo in the treatment of depression.³¹ Another NMDA receptor, CP-101 606, binds to the NR2B subunit of the NMDA receptor and has less dissociative effect than ketamine. A single infusion of CP-101 606, unlike an infusion of placebo, decreased depression for up to 4 days.³² Another NR2B antagonist, MK-0657, was given orally for 12 days in a placebo-controlled crossover study in patients with treatment-resistant depression.³³ Although the drug did not cause more dissociative symptoms than placebo, it also did not have a significant therapeutic effect, as assessed by the primary outcome measure. This is not surprising given that only 5 patients were treated. While interesting, these studies do not shed much light on the possible role of expectancy in the therapeutic effect of ketamine.

The need for further clinical trials

For botulinum toxin, the main need is for a trial replicating its antidepressant effect. Preferably this should have a better

placebo control, as outlined previously, and should include some measure of the expectations of patients. In the original study, presumably patients consented to participate only if they desired botulinum toxin treatment anyway or had definite expectations about its success. Given the existence of 1 positive study, it should be possible to recruit a more representative group of depressed patients.

For psilocybin, most studies so far have been on healthy participants, and there is a need for more studies on patients. The problem here is to select patients with symptoms that might plausibly be helped by psilocybin. Currently www.clinicaltrials.gov (accessed June 12, 2012) lists 3 trials with psilocybin that are recruiting patients: 2 controlled trials in cancer patients with diagnoses of anxiety or depression, and 1 open study on patients with alcohol dependence. A recent meta-analysis of 6 studies published between 1966 and 1970 using a single dose of lysergic acid diethylamide to treat alcoholism found a significant therapeutic effect for up to 6 months after treatment, although the effect was no longer significant at 12 months.³⁴ This provides a good rationale for testing psilocybin in individuals with alcoholism.

Future studies need to assess to what extent psilocybin may have adverse effects, either acutely or in the long term, and what predictors may explain adverse effects. Assessing results from a number of studies, Studerus and colleagues³⁵ found that unpleasant and/or anxious acute reactions to psilocybin were most strongly associated with emotional excitement and young age and were most often observed in studies involving positron emission tomography. This suggests that a calm setting during psilocybin administration may be useful. In a follow-up assessment at 8–16 months of 90 healthy people who received psilocybin in experimental studies, 7 participants reported they had experienced negative changes in well-being due to the psilocybin.²⁶ Future studies need to look at factors associated with these long-term adverse effects.

For ketamine, the main need is for clinical studies that will test more adequately whether, or to what extent, the effect of ketamine could be a placebo effect. Two approaches that might provide useful information are using a positive placebo and conducting controlled studies investigating whether repeated ketamine administration every few days would prolong its effect. If it is a placebo effect, the antidepressant action might be expected to diminish after repeated doses.

Implications and unanswered questions

The antidepressant effect of botulinum toxin, if real, is not the first example of how input from the periphery to the brain can influence mood. Vagal nerve stimulation is a well-established antidepressant treatment. Most of the afferent fibres in the vagus nerve are from the viscera. However, there is no understanding of what fibres are responsible for the antidepressant effect and why stimulation of input normally coming from the viscera (if that is what is responsible) should have an antidepressant effect. Vagal nerve stimulation is just one of a number of techniques, with antidepressant action, for stimulating the brain. Exercise is known to improve mood, and can have

an antidepressant effect. However, the extent to which the effects of exercise are mediated by neural inputs to the brain or via factors in the blood is not known. Unlike vagal nerve stimulation and exercise, botulinum toxin decreases input to the brain, rather than increasing it, and does so in a very specific manner. If the antidepressant effect of botulinum toxin is confirmed, it should help focus research on more specific peripheral inputs. One potential line of research is to look at the implications of contracting the zygomaticus major or the risorius muscles that are used in smiling. An experimental design similar to that of Hennenlotter and colleagues,²⁵ described previously, might reveal the areas of the brain activated by the use of the muscles involved in smiling. A related question is whether teaching people to contract their zygomaticus major and the risorius muscles regularly would potentiate the effects on mood resulting from inhibition of the corrugator muscles.

Of the trio of potential treatments discussed here, botulinum toxin is obviously very different from the drug treatments. While its therapeutic effect, if real, occurs after a single treatment, that treatment inactivates the facial muscles involved in frowning for months. The therapeutic effects of psilocybin and ketamine must be due to changes in the brain that occur during the brief period when the drug is present in the brain. Some of the acute effects of psilocybin on the brain are reasonably well understood. As discussed in recent reviews, an important component of hallucinogenic action, including that of psilocybin, is agonism at 5-HT_{2A} receptors.^{36,37} The hallucinogenic action of psilocybin is blocked by the relatively specific 5-HT_{2A} antagonist ketanserin. Carhart-Harris and colleagues³⁸ studied healthy volunteers who received psilocybin while being studied with fMRI. Only decreases in blood flow were seen, and the magnitude of the decrease in the anterior cingulate cortex/medial prefrontal cortex was related to the subjective effects. Psilocybin also caused a significant decrease in the positive coupling of the medial prefrontal cortex and the posterior cingulate cortex. The authors suggested that their results imply that “the subjective effects of psychedelic drugs are caused by decreased activity and connectivity in the brain’s key connector hubs, enabling a state of unconstrained cognition.” The important but unanswered question is how a state of unconstrained cognition might cause changes in attitude and behaviour more than a year later. This is more likely to be explained by psychology than neurobiology. There are other examples, such as posttraumatic stress disorder, of how a temporary mental state can have profound long-term effects. Of course a long-term change in someone’s perception of the world and her/his place in it may have important biological effects. Mindfulness meditation is designed to alter peoples’ perception of the world by making them disengage from ruminations and attention to negative thoughts and become aware of and accept thoughts nonjudgmentally without trying to change them.³⁹ An 8-week course of mindfulness meditation increased grey matter in brain regions involved in learning and memory, emotion regulation, self-referential processing and perspective taking in healthy people.⁴⁰ In stressed individuals, the decrease in perceived stress after an 8-week course of mindfulness meditation was associated with a decrease in the right basolateral amygdala grey matter den-

sity.⁴¹ If the changed perception of the world brought about by mindfulness meditation over a period of 8 weeks can cause changes in the brain, this raises the possibility that the change in perception due to psilocybin may result in changes in the brain over a matter of weeks. How such brain changes may interact with the changes in psychology is not known. There is need for more work on the long-term psychological changes associated with psilocybin, as well as research on the long-term brain changes and their possible association with the psychological changes.

Ketamine is of interest both because of the rapid onset of its antidepressant action and because of the lasting effect of a single dose. So far, insights into the biological mechanism involved in ketamine’s rapid action are derived from brain scans of healthy people after ketamine administration, which are consistent with the idea that ketamine acts by rapidly increasing function in the prefrontal cortex and anterior cingulate cortex.¹² Insights into its action beyond the time of administration are derived from work on rodents, suggesting the involvement of synaptic plasticity and neurotrophic signalling.^{12,42} For example, Li and colleagues⁴³ used a rat model in which chronic, unpredictable stress decreased the expression of synaptic proteins and excitatory postsynaptic currents in layer V pyramidal neurons in the prefrontal cortex. Two days after a single dose of ketamine, these changes were reversed. What is needed now are studies of changes in psychological and brain function in depressed patients a few days after a single treatment of ketamine.

The 3 treatments discussed in this article are of interest because, if confirmed, they are examples of how single treatments can have a lasting effect. The rationale for their use is very different. For psilocybin the rationale was derived from a long tradition of hallucinogen use in various cultures, for ketamine it was primarily animal research, and for botulinum toxin it was based on research involving healthy individuals. The treatments are also very different in their effects, and there does not seem to be a unifying theme that could guide research. Nonetheless, these treatments are instructive for several reasons. First, they act through mechanisms that get relatively little attention in the search for improved therapeutic interventions. Second, the side effects, following the initial effects in the case of ketamine and psilocybin, do not seem to be substantial. Third, the possible effect of botulinum toxin suggests that peripheral inputs to the brain can be used with great specificity to produce therapeutic effects. Fourth, in the case of psilocybin, although the initial effects are pharmacologically induced, the long-term changes may be more psychologically mediated. More research at the intersection of pharmacotherapy and psychotherapy may be fruitful.

Competing interests: None declared.

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