Herbal Treatments for ECS-Induced Memory Deficits: A Review of Research and a Discussion on Animal Models

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SUMMARY
During the last decade the use of herbal medicinal substances in the attenuation of anterograde and retrograde amnesia induced by electroconvulsive shock (ECS) has been studied using animal research. We will discuss the background of herbal medicine in India, review the research findings on herbal medicines for ECS-included amnestic deficits, and examine the applications and limitations of animal models in this context. We will focus on our own research and insights, with particular emphasis on practical issues.

Key Words: Amnesia; Animal models of learning and memory; Cognition; Electroconvulsive shock; Electroconvulsive therapy; Herbal medicine; Memory.

Electroconvulsive therapy (ECT) is associated with anterograde and retrograde amnestic deficits that can, in certain cases, be severe, persistent, or both (Abrams, 1997). Several pharmacological treatments have been suggested to reduce such deficits, but in general the results have been disappointing (Andrade, 1990; Krueger et al., 1992; Nobler and Sackeim, 1993). In recent years, studies have explored the antiamnestic efficacy of herbal medicines in the context of animal models of ECT (Andrade, 1995). This paper will briefly introduce the practice of herbal medicine in India, summarize the studies that have examined herbal attenuation of amnestic deficits induced by electroconvulsive shocks (ECS), and discuss the application and limitations of animal models in the context of such research.

Herbal Medicine and its Practice in India
Systems of herbal medicine are practiced in traditional societies in many parts of the world; allopathic science may gain much from the study of such systems. Several important allopathic drugs, such as digitalis, quinine, and atropine, originated from plant sources; psychiatrists need no reminding that over half a century ago, the (Indian) herbal pharmacopoeia contributed reserpine to modern medicine. The need to study the psychotropic properties of herbal drugs is recognized even in developed societies: for example, clinical research on St. John’s Wort was recently reviewed in the British Medical Journal (Linde et al., 1996), and a multicenter study on the efficacy of an extract of Gingko biloba in patients with dementia was recently published in Journal of the American Medical Association (JAMA) (Le Bars et al., 1997). During November 1998, an entire issue of JAMA was devoted
to articles on alternative systems of medicine including herbal treatments.

American laboratories are already screening individual herbs for psychotropic potential: the United States’ efforts in this regard have been summarized by Cott (1995). By way of example, Cott et al., (1994) reported that extracts from *Withania somnifera* show high affinity for GABA receptors, and that extracts from *Centella asiatica* show affinity for CCK receptors. *Withania somnifera* and *Centella asiatica* are known as Ashwagandha and Mandookaparni (respectively) in Ayurveda, which is a traditional system of medicine in India. Since GABA agonism and CCK antagonism have been linked to anxiolysis, these findings support the recommendation in Ayurveda that Ashwagandha and Mandookaparni be used as sedatives (Handa, 1995).

The discipline of Ayurveda has existed in India for millennia. One of the practices of Ayurveda is to treat poor health with medicines obtained from herbs. These medicines are prepared from the leaves, roots, or other parts of certain plants. The medicines are most commonly dispensed in the form of a powder or as a water-based extract that is prepared as a decoction, much as tea is brewed. Indian herbal substances with psychotropic properties have been described by Iyengar (1981), Satyavati (1995), Dhawan (1995), and Handa (1995).

Ayurvedic medicine is widely practiced in India to this day. Students receive their training in Ayurvedic medical colleges, and are subsequently licensed by the state to practice their art. Their training and licensing is independent of and parallel to the training and licensing of allopathic practitioners.

The Indian government as a policy encourages Ayurvedic and other forms of indigenous medicine (such as Unani and Sidda). One of the forms of encouragement is to permit the marketing and prescribing of herbal medicinal substances with no prior requirement that these substances be demonstrated to be effective and safe. All that the Drug Controller of India requires, in fact, is evidence that the substances in question have been recorded to have medicinal properties in the ancient Indian literature. In contrast, allopathic drugs introduced into the country must pass through clinical trials before their marketing is permitted; this requirement is not relaxed even if the drug has been approved of for marketing in the developed world.

Ayurvedic clinicians classify and diagnose illness in a manner that is radically different from that followed in allopathy; concepts in the field of mental health have been described by Ramachandra (1990). Furthermore, Ayurvedic clinicians do not have adequate training in the design, conduct, and analysis of clinical trials. As a result, they do not engage themselves in research that is of a nature that allopathic medical journals will find acceptable. In consequence of this, and in consequence of the policy of the Drug Controller of India, a very large number of herbal medicines and formulations thereof are commercially marketed and prescribed in the country without evidence of efficacy and safety. In general, however, experience suggests that adverse effects are not an issue because patients hardly ever
experience ill effects when receiving herbal medicines; what remains in question is whether these medicines are effective at all.

The study of the Indian herbal pharmacopoeia through clinical trials is an expensive, laborious, and time-consuming option. The logistics of conducting clinical trials on herbal medicines are further complicated by two factors: most herbal pharmaceutical companies are too small to be able to afford to commission clinical trials, and the larger companies are not interested in clinical trials because their products have already been licensed for sale. Interested scientists are therefore compelled to resort to animal models for the efficacy screening.

EFFICACY SCREENING
Where Should One Begin?
Our interest in the herbal attenuation of ECT-induced cognitive impairment arose in the early 1990s. We were faced with a wide choice of individual substances, all of which were described in Ayurveda to enhance central nervous system functioning; these substances included Shankapushpi, Brahmi, Ashwagandha, Mandookaparni, and others (for review, see Iyengar, 1981; Dhawan, 1995; Handa, 1995; Satyavati, 1995). We were also faced with a wide choice of commercial formulations comprising combinations of various substances in various proportions; these formulations were marketed with the assertion that individual ingredients complement each other in efficacy and cancel out each other in adverse effects (this assertion is a common philosophy underlying Ayurvedic medical practice).

We considered it appropriate to commence our studies with a formulation rather than with an individual herb because a formulation, comprising several ingredients, is more likely to contain a biologically useful chemical, and is therefore more likely to yield positive results. As the starting point for our research, we selected the most popular procognitive formulation (Mentat) marketed by the largest herbal pharmaceutical company (The Himalaya Drug Company) in the country.

Mentat
Mentat is also known as BR-16A. It contains over 20 different ingredients; the exact formulation differs between pediatric and adult presentations of the composite. Important ingredients of BR-16A, suggested to improve memory function, include the following: Jal-brahmi (*Bacopa monnieri*), Mandookaparni (*Centella asiatica*), Ashwagandha (*Withania somnifera*), Shankapushpi (*Evolvulus alsinoides*), Jatamansi (*Nardostachys jatamansi*), Vach (*Acorus calamus*), Malkangni (*Celastrus paniculatus*), and Sonth (*Zingiber officinale*). Other ingredients of BR-16A, claimed to be “nerve tonics”, include Tagar (*Valeriana wallachii*), Badam (*Prunus amygdalus*), Salap (*Orchis mascula*), Lavang (*Syzygium aromaticum*), and Pearl (*Mukta pishti*). The remaining ingredients are putative general tonics and vitalizers (The Himalaya Drug Company, 1991).

We examined the cognitive benefits with Mentat (200 mg/kg/day) using a food-motivated
paradigm in food-deprived rats studied in the Hebb-Williams complex maze and in the T-maze. In the former task, each rat was trained to leave a start chamber, traverse corridors in the maze, and locate the reward chamber; the learning score was the time taken by the rat to reach the reward chamber. In the latter task, each rat was taught to leave the stem of the T-maze, choose between correct and wrong arms of the maze, and locate the reward chamber at the end of the correct arm; the learning indices were the number of trials taken by the rat to achieve a criterion that defined satisfactory learning, and the number of wrong arm entries during this period.

The results were encouraging. We found that 3 weeks of administration of Mentat significantly improved Hebb-Williams maze learning in rats (Joseph et al., 1994). This established the potential of Mentat as a procognitive formulation worthy of examination in the context of ECT-induced cognitive dysfunction. We next showed that in an identical experimental design, Mentat attenuated anterograde amnestic deficits induced by six once-daily ECS (Joseph et al., 1994). In a second study, we found that rats that were pretrained in the Hebb-Williams and the T maze tasks, and which received six once-daily ECS, learned better during post-ECS re-exposure to the same tasks if they had received Mentat for 2 weeks than if they had received placebo (Andrade et al., 1994a). It is uncertain, however, whether Mentat improved renewed learning, or enhanced retention of learning during the first (pre-ECS) exposure to the-tasks, or both. In a third study, we found that the administration of Mentat for approximately 1 week to rats pretrained in the T maze resulted in an attenuation of the retrograde amnestic deficits induced by two ECS administered on the same day, 5 hours apart (Andrade et al., 1995). In the most elaborate study of all, we employed the Hebb-Williams maze to confirm that approximately 2 weeks of treatment with Mentat enhances the ability of rats to learn the task as well as attenuates both retrograde and anterograde amnesia induced by two once-daily ECS (Faruqi et al., 1995).

Results in healthy rats may not be generalizable to dysfunctional humans. In an attempt to make the animal model more representative of situations of clinical impairment, we preselected rats for poor learning on the Hebb-Williams maze and examined whether the administration of Mentat for 3 weeks could attenuate the anterograde amnestic effects of six once-daily ECS; the results again supported the use of Mentat (Ramteke et al., 1995).

We have not been able to offer any convincing explanation for the mechanism of procognitive action of Mentat. In only one of the studies described, we found that Mentat produced a small but statistically significant abbreviation of the ECS seizure duration (Faruqi et al., 1995). This finding was in line with unpublished data furnished by the drug company that Mentat shortens chemically induced seizures, and abbreviates breakthrough seizure duration in epileptic patients on antiepileptic medication. In this study, however, seizure duration showed no statistical relationship to the learning performance of the rats, suggesting that the mild anticonvulsant effect of Mentat did not directly or indirectly mediate its antiamnestic effects.
In another study, we used *in vivo* chemical challenges in rats to demonstrate that Mentat enhances dopamine postsynaptic receptor functioning, but does not influence the activity of dopamine autoreceptors or alpha-2 noradrenergic receptors (Andrade *et al.*, 1994b). The relevance of these findings to the procognitive effects of Mentat requires further study.

**Memorin**
As already described, Mentat is a complex herbal formulation. With the expectation that not all of its contained ingredients are relevant to its procognitive actions, we searched for simpler formulations to study, and finally chose Memorin (Phyto-Pharma). This formulation is derived from Mandookaparni (*Centella asiatica*), Jatamansi (*Nardostachys jatamansi*), Yashtimadhu (*Glycyrrhiza glabra*), Shankapushpi (*Evolvulus alsinoides*), and a subformulation, Smruti Sagar. While Memorin is not exactly a subset of Mentat, there is considerable overlap in the contained ingredients.

We examined the cognitive benefits with Memorin (200 mg/kg/day), using T maze as in the Mentat studies and using a passive avoidance paradigm. In the latter experiment, each rat was trained to remain in the bright chamber of a shuttle box to avoid receiving an electric shock in the dark chamber; the duration for which the rat remained in the bright chamber was its recall score.

As with Mentat, the results with Memorin were encouraging. The administration of Memorin for 2 weeks attenuated retrograde amnesia, measured using the passive avoidance paradigm, in rats that received two ECS on the same day, spaced 5 hours apart (Vinekar *et al.*, 1998). Likewise, 2 weeks of Memorin attenuated the anterograde amnesia induced by two ECS (again administered on the same day, 5 hours apart) and measured in the T maze (Andrade *et al.*, 1999). In neither study did Memorin influence the ECS seizure duration. As with Mentat, we were unable to suggest any mechanism for the procognitive action of Memorin.

Our experience with Memorin in elderly subjects diagnosed with age-related cognitive decline (DSM-IV) has been very encouraging. Memorin capsules administered four per day in two divided doses produced significant improvements in several measures of memory relative to placebo (Andrade *et al.*, 1998). A small pilot study comparing Memorin and placebo in patients receiving ECT has recently been completed, and the data are presently under analysis.

**Shankapushpi**
Shankapushpi (*Evolvulus alsinoides*) is an ingredient of both Mentat and Memorin. Shankapushpi is highly rated in Ayurveda as a treatment for impairments related to the central nervous system. Accordingly, we examined the ability of an aqueous extract of Shankapushpi to promote learning, and to attenuate ECS-induced anterograde and retrograde amnesia studied using the T-maze and the Hebb-Williams maze.

The results were altogether disappointing. Shankapushpi did not enhance learning
performance on either task, nor did it attenuate either anterograde or retrograde amnesia induced by various schedules of ECS in rats (abstracted in Andrade et al., 1996). It is of course conceivable that Shankapushpi may contain a procognitive ingredient that does not emerge in an aqueous extract; if so, an alcoholic extract of Shankapushpi, or extracts obtained by some other process, may yield more encouraging results; this issue will require evaluation in future experiments.

Caveats
Herbal medicines are prepared from the leaves, roots, and other parts of specific plants. The biology of these plant parts varies as a function of their location on the plant, the time of day, the season of the year, the cultivation process, variations in weather and soil, and other factors. Accordingly, standardization of an herbal pharmaceutical product requires much care.

Today, the principal chemical ingredients of most of the important herbal source materials are known and have been published (e.g., Kirtikar and Basu, 1993; 1994). What is uncertain, however, is the identity of the chemical that is biologically relevant in a particular herb. Most herbal pharmaceutical companies therefore obtain a chromatographic “fingerprint” of a gold standard of their herbs, and endeavor to ensure that all subsequent batches of their product match this fingerprint. The shortcoming of this procedure is that the standardization process may be based upon irrelevant ingredients.

ANIMAL MODELS OF COGNITION: THEORETICAL AND PRACTICAL ISSUES
Animal models of cognition are well described in the literature and will not be reviewed here. Instead, we present certain theoretical and practical issues that arise from the conduct and interpretation of research based on such models. We focus on our own experiences in this regard, derived from the studies described in the earlier section.

General Limitations of Animal Models
Conducting research on human subjects may yield the most reliable results, but is expensive, time-consuming, and fraught with ethical difficulties. The use of animal models of physiological or psychological function or dysfunction is therefore helpful during the early stages of hypothesis generation, during drug development, and in other contexts of explorative research. The utility of animal models notwithstanding, it must be remembered that resulting findings are generalized to human contexts; this exposes the limitations of such models. Consider the following issues:

1. A rat is far removed from a human; the validity with which comparisons can be drawn between rodent and human research is therefore uncertain. For example, the complex processes described under registration, retention, recall, and recognition under short- and long-term storage conditions in humans may not apply to the same extent in rats. The neurophysiology and neurochemistry of a rat may be simpler than that of a human, making it easier for a drug to have a demonstrable procognitive effect in the former
than in the latter situation. A contrary view is also conceivable: A complex human system may have more sites at which a multi-ingredient herbal compound could act, making the compound more likely to be effective in the human context than in the laboratory context.

2. A healthy rat is far removed from a dysfunctional human. For example, even if memory processes are identical in rats and humans, it is uncertain whether memory processes in healthy rats are similar to memory processes in humans who are modified by conditions such as depression and schizophrenia. It is likewise uncertain whether a drug that has procognitive effects in a healthy rat will have procognitive effects in a human whose biology is compromised by the neurophysiological, neurochemical, and neuroendocrine changes associated with psychiatric illness.

3. Even if healthy rats can be equated with dysfunctional humans, animal models of psychological states are still remote approximations of what they are clinically considered to represent. For example, the processes that delay a rat’s ability to locate the reward chamber in the Hebb-Williams maze are likely to be much different from the processes that underlie ECT-induced autobiographical memory impairment, if only because maze learning is a spatial task while autobiographical memory is nonspatial. A drug that is effective in one context may therefore not be effective in the other context.

4. Even if animal models correspond perfectly with the human processes that they are desired to represent, the absence of internal and external “noise” in laboratory contexts prejudices the generalizability of animal studies. For example, laboratory animals used in research usually belong to the same age, sex, and inbred strain; they therefore closely resemble each other in behavior. Furthermore, the laboratory environments in which the animals are housed and the experiments conducted are both carefully controlled, and are kept constant all through the experiment. All these factors reduce the variance of the results in animal experiments. In contrast, in human contexts interpersonal and environmental differences across subjects are multiple and are very difficult to control. These factors increase the variance of results in clinical research. The consequence of low variances in animal research and high variances in clinical research is that statistical significance is far more easily attained in the laboratory than in the clinic. Thus, for example, a drug that has a small procognitive effect may produce statistically significant results in the laboratory and insignificant results in the real world. In other words, the small positive effect of the drug is, in human research, drowned out by the background noise. This may be one of the reasons why many procognitive treatments that have been shown to be effective in animal models prove to be ineffective in clinical trials. A point worth noting is that small positive effects, if they exist, can be demonstrated in clinical contexts if a sufficiently large sample is studied; however, it is uncertain whether the statistically significant results so obtained would be clinically meaningful.

Thus, it is necessary to generalize with caution between animal and clinical research; when such generalizations are made, the limitations of animal models must be kept in mind.
General Biases that Operate in Animal Models of Cognition

Measures of cognition in animal models may be influenced by biasing factors that are unrelated to cognition. Such factors include motivation, motility, and left-right preferences.

An animal must be adequately motivated to attempt a cognitive task and to do well on it. In other words, performances that are deemed to represent learning efforts must be driven by motivation to learn rather than by random, exploratory behavior. Motivation is generally ensured through reward (e.g., a food pellet) or punishment (e.g., a footpad electric shock). Food-motivated tasks may require the rat to be on 1 hour/day restricted feeds for 2-3 days prior to the learning experiments; feeding on the days on which learning is assessed is permitted after the learning tasks for the day have been completed (If the learning tasks span several days, it may be advisable to permit feeding only when several hours have elapsed after exposure to the task; otherwise, the rat may show poor motivation to attempt the task, having already learned that food will be provided after exposure to the task).

A problem with such food deprivation is that the rat may become sluggish; as a result, the rat may not attempt the task at all. For example, we have observed that rats on restricted feeds sometimes do not move out of the stem of the T maze. The learning of these rats cannot be assessed, and the results of the experiment may consequently suffer bias. Rats that are sluggish but that do attempt the task may show biased performances on time-based variables. Another problem with food deprivation is that hypoglycemia can itself compromise learning. The interaction between this variable and the experimental variable cannot be estimated. These limitations of food-motivated tasks with rats on restricted diets must be kept in mind when conducting and interpreting research based on such paradigms.

Learning tasks that are time dependent are biased by variations in basal animal motility. For example, in the Hebb-Williams maze, the dependent variable that estimates learning performance is the speed by which the rat reaches the reward chamber. This variable is influenced by the rat’s basal motility: a sluggish rat will “learn” more slowly while a restless rat will “learn” more quickly. Hence, a treatment that alters basal motility will produce spurious changes in learning performance. The direction of the error will depend on the nature of the task and the effect that the treatment has on motility. A treatment that decreases motility will falsely enhance learning performances and will fail to adequately identify amnestic effects in learning tasks, such as passive avoidance paradigms, in which an absence of response from the animal indicates learning. Such a treatment will fail to adequately identify learning, and will falsely inflate amnestic effects in learning tasks such as the Hebb-Williams maze and active avoidance paradigms, in which an active response from the animal indicates learning. Treatments that increase motility will produce errors in the opposite direction. For example, Posluns and Vanderwolf (1970) found that retrograde amnesia in passive avoidance tests after ECS may be partly due to a deficit in the ability to suppress motor activity.

Possible solutions to motility-related problems in time-based learning tasks are either to
previously study and rule out an effect of the treatment upon basal motility before proceeding with the task or to use a task such as the T maze, the results of which are not influenced by motility factors. Another possibility is to deliberately use a learning task that predisposes to a false negative error when studying a putatively procognitive drug that affects basal motility. The logic here is that it may be better to err on the side of caution during screening. While including a sham treatment control group by itself will not help, the use of a factorial experimental design can reduce (but not necessarily eliminate) motility related errors. In a study intended to test the antiamnestic effects of a drug in ECT-treated animals, the experiment would include drug/ECT, sham drug/ECT, drug/sham ECT, and sham drug/sham ECT groups. The last two groups serve as internal controls to the main experimental and main control groups. In the analysis of results, the interaction effect between the drug and ECT would indicate the antiamnestic action of the drug.

Many of the ingredients of the herbal formulations that we studied are claimed to have tranquilizing properties and would consequently be expected to reduce motility. We therefore focused on T maze paradigms in our recent research and used factorial designs in all our studies to minimize motility-related errors.

For over two decades it has been recognized that rats show clear left-right preferences, and it has recently been recognized that these preferences influence rats’ choices on spatial tasks such as the T maze. Very recently (Andrade et al., unpublished observations), we showed that the bias in T maze arm preference was substantial: 22.2% of the rats that we studied showed a left preference, and 52.8% showed a right preference. This bias was spontaneous and was consistent over two testing sessions 30 days apart. Left- and right-biased rats learned rapidly when trained to enter the arm ipsilateral to the bias; learning was significantly poorer or did not occur contralaterally. This contralateral learning difficulty was particularly evident when transfer of learning was assessed, especially with right-biased rats. Interestingly, unbiased rats (25%) also showed some difficulties in attaining the criterion for learning in one or the other arm of the T maze. This finding is probably a result of the broad definition that we used for absence of bias in contrast with the strict definition used for the presence of bias. Actually, some of the unbiased rats also showed bias albeit to a lesser extent, and this bias may have been responsible for the learning confusion observed. Our findings suggest that unless spontaneous laterality preferences are taken into consideration, spurious results may be obtained in spatial learning tasks.

In our own research, described in an earlier section, we attempted to ensure validity of results by screening all rats for the ability to learn in both arms of the T maze, and by randomizing rats into groups based on their learning performances. We consider that there are three prerequisites for valid use of the T maze in cognitive research: Animals should be preselected for capacity to learn in both arms, randomization into experimental and control groups should be stratified for spontaneous arm bias, and original learning should be directed towards the arm contralateral arm. These prerequisites are unfortunately likely to make T maze research time-consuming and unattractive.
General Precautions Necessary in Animal Models of Cognition

Many obvious precautions are described to ensure that performances on learning tasks are not biased. For example, studies are best conducted on young adult male rats. Rats that are not adults have immature nervous systems and may not learn consistently. Rats that are too old have age-related impairments that compromise their learning performances. Female rats experience estrus every 5 days, and their learning behavior may be influenced as a function of their hormonal status.

Rats should be obtained from the same batch for the entire study, otherwise heterogeneity across batches may confuse results. While the use of an inbred strain may to some extent ensure uniformity, there is no assurance that even within an inbred strain rats will be uniform in their behavior on a particular task (Pradhan et al., 1990). Only naïve rats should be selected for experiments; rats that have been used in an earlier experiment are likely to show biases in behavior. The rats must be uniformly treated in matters ranging from housing to handling and feeding. If rats belonging to different experimental groups are treated differently, differing performances may be attributable to such differences in treatment rather than to differences in learning. The rats should be housed and maintained in reasonable comfort. Rats that are isolated one per cage, or that are otherwise stressed may perform poorly as a function of such stresses.

Rats should be handled regularly so that their responses to a learning task are not biased by the stress of the handling during the experiment. Rats should be familiarized with the experimental apparatus prior to the actual experiment so that their performances are not biased by exploratory behavior. The experiment must be conducted in an environment that is relatively sound proof and free from other distractions. The researcher must be seated such that his or her presence does not distract the rat. External stimuli, including lighting, should not cue the rat. Lighting in particular should be kept constant all through the study, because rats are very light sensitive, and become less or more motile with more and less environmental brightness, respectively. The apparatus must be cleaned after every rat has completed its task, otherwise the scent markings of the rat will bias the performances of future rats exposed to the apparatus. Learning assessments must be conducted at the same time of day lest circadian rhythm variations bias results. These and other precautions are well described in most textbooks on laboratory procedures (Bures et al., 1976; Joseph and Waddington, 1986; Van Ree and de Wied, 1988).

One further precaution deserves special mention. In animal research, rats are frequently assigned to one of several different groups. It is generally not feasible to complete an entire experiment in a single day; therefore, for convenience researchers sometimes execute their study by testing one group at a time. The fallacy of this procedure is that it permits the entry of sampling, handling, environmental, and other biases into the study. A more appropriate way of conducting the experiment is to ensure that each group is proportionately represented in each session of work.
ECS AND ANIMAL MODELS OF COGNITION

Models of ECS-induced Amnesia

The literature on ECS and learning in animal models has been reviewed by Krueger et al., (1992) and Fochtmann (1994). This section will therefore provide only a brief summary. Retrograde amnesia associated with ECS has been studied most commonly using the passive avoidance paradigm (e.g., Alpern and McGaugh, 1968). Conditioned taste aversion has also been employed as a model (e.g., Shaw, 1986). Active avoidance, appetitive or aversive water reinforcement, bar pressing, conditioned emotional responses, T- and Y-maze learning, brightness discrimination, and hunger-fear conflict responses are some of the other paradigms that have been used to assess retrograde amnesia after single or repeated ECS (Fochtmann, 1994).

Anterograde amnesia with single or multiple ECS has been less extensively studied. Again, the most common method employed has been the passive avoidance paradigm (e.g., Gardner et al., 1972). Several other models of learning have also been described. Not all have succeeded in eliciting amnesia (Fochtmann, 1994). A general observation has been that the ability of ECS to prevent an association from occurring initially is more pronounced than its ability to disrupt an already formed association (Kral and Beggerly, 1973).

The method of ECS administration has been shown to affect the degree of memory impairment. Corneal electrode placement is associated with greater amnestic effects than transauricular electrode placement (Dorfman and Jarvik, 1968). Brief-pulse ECS is associated with less severe memory impairment as compared with sine wave stimuli (Docter, 1957). Altering the convulsion with the use of either anesthesia or nonconvulsive stimulation has variable effects on ECS-induced memory deficits. Increasing the number, frequency, intensity, or duration of ECS, or the proximity of the ECS to the time of training or testing, is associated with a greater degree of memory impairment (Fochtmann, 1994). These issues need to be kept in mind when choosing a model.

Practical Issues

Genetic differences influence task learning, and both good- and poor-learning strains have been discussed (Roullet and Lassalle, 1995; Van Buskirk and McGaugh, 1973). For example, C57BL/61bg mice are good learners in conditional spatial alternation tasks, while DBA/21bg mice are poor learners and require at least twice the number of training trials (Paylor, 1993). When an inbred strain of rats is unavailable, there is variation in learning behavior across batches of rats as well. Thus, previous experiences and textbook descriptions of animal models of cognition notwithstanding, prior to each experiment each laboratory may need to restandardize the model of learning and ECS-induced amnesia, readjusting variables ranging from the extent of pre-ECS training and the magnitude of aversive shocks to the strength, number, and frequency of ECS stimuli.
Administration of unmodified ECS may lead to spinal fracture and paraplegia in a small percentage of rats. In our experience, the risk is greater in very young animals and when higher stimulus doses are used; however, old animals and those with greater muscle mass are also at risk. Administration of modified ECS is difficult. Ventilating a paralyzed rat before and after the ECS poses problems, and the use of anesthesia may enhance the ECS-induced cognitive deficits (Miller et al., 1985). While the latter may be desirable because it makes the model more representative of clinical contexts, results may actually be inconsistent. Some studies have reported less amnesia with the use of anesthesia, and even the elimination of convulsion (Fochtmann, 1994).

Making an ECS schedule representative of clinical contexts is not easy. We have observed that the administration of alternate-day ECS does not reliably induce amnesia with the models of cognition that we have studied. In this regard, models of retrograde amnesia pose particular problems. The number and frequency of the ECS administered must ideally mimic a clinical course of treatments; however, employing such a schedule of ECS risks introducing time-dependent forgetting of pre-ECS learning. We have therefore administered daily ECS, and sometimes even twice daily ECS, with the (unproven) assumption that the mechanisms of ECS-induced amnesia are similar, provided that the number and frequency of ECS do not differ too widely from clinical norms.

Care must be taken to ensure that the interval between the administration of ECS and subsequent exposure of the rat to the learning task is consonant with the aspect of memory that is being studied. Early exposure to the task is relevant to the transient, postictal cognitive effects of ECT while later exposure is relevant to the more enduring deficits.

Finally, just as learning assessments are best conducted at a fixed time of day, ECS should ideally be administered at a fixed time. This is because variations in ECS-induced seizures have been noted at various points in the diurnal cycle. These variations have been attributed to endogenous opioid levels (Oliverio et al., 1985).

**CONCLUSION**
In this article, we have briefly introduced the practice of herbal medicine in India, summarized the studies that have examined the herbal attenuation of amnestic deficits induced by ECS, and discussed the application and limitations of animal models in the context of such research. We have primarily focused on our own work and insights, and have also examined practical issues that are involved in studies of this nature. For a comprehensive review of the effects of ECS on memory and cognition, the effects of pharmacological agents on ECS-induced memory deficits, and the effect of co-administered drugs on ECS seizure properties, the reader is referred to Krueger et al. (1992) and Fochtmann (1994).

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