A reexamination of flurothyl infusions holds promise for improved resolution of severe mood disorders, as well as for a greater understanding of the mechanism of their pathophysiology.

A Hollywood movie almost killed an important psychiatric treatment. After clinicians and members of the public saw the film *One Flew Over the Cuckoo’s Nest*, which premiered in 1975, many swore “never again.” The fantasy bore no relationship to the actual conduct of an effective psychiatric treatment, yet almost wrote its death warrant.

Years later we are still dealing with the fallout from that fantasy. Although many clinicians have accepted ECT, the public harbors the image of Jack Nicholson being forcibly subjected to treatment without his informed consent, and they do not wish this for one of their family members. As a consequence, serious cases of depression, mania, and catatonia—unresolved by medications and psychotherapies—are haphazardly denied evidence-based treatment. The effective component of the treatment is the cerebral seizure itself and not the electricity. There are other ways of eliciting seizures, however, without putting electrodes on fearful patients. Flurothyl, an anesthetic, offers an effective treatment by inhalation or by infusion. Chemical infusions to treat MDD began in the late 1950s, as soon as the antidepressant efficacy of oral imipramine was recognized. Rapid relief was temporary, and adverse effects of dry mouth and skin, increased heart rate, and impaired vision deterred its use. In 1982, the Swiss psychiatrist Paul Kielholz optimistically reviewed infusion therapy with an emphasis on the antidepressants clomipramine and maprotiline. Brightening of mood occurred but was transient, and the procedure was discarded. Recently, infusions of the anesthetic ketamine have been tested but, again, the benefits are short-lived.

Studies from the 1930s found minimal concentrations of brain glia in those who died with schizophrenia and a surfeit in those with epilepsy. A concept of an antagonism between these disorders encouraged the search for ways to safely induce seizures. Introduced in 1934, intramuscular injections of camphor were successful, but dosing was difficult and the delay to seizure was worrisome. Many injections failed to elicit a seizure. Intravenous pentylenetetrazol (Metrazol) was tested the same year and quickly adopted because of its greater efficiency. By 1938, the induction of seizures by electricity was found to be more efficient, giving rise to the worldwide use of ECT.

In 1957, an alternative seizure-inducing agent, flurothyl (Indoklon), a congener of the inhalant anesthetic diethyl ether, was tested. With a few inhalations consciousness was lost, and with a few more the electroencephalogram (EEG) showed the slow waves and spikes characteristic of a seizure. Extensive clinical experiences and 4 well-documented controlled trials comparing flurothyl with ECT reported that from 3 to 10 inhalations over a few weeks successfully relieved severe depression and psychosis. In 1957, an alternative seizure-inducing agent, flurothyl (Indoklon), a congener of the inhalant anesthetic diethyl ether, was tested. With a few inhalations consciousness was lost, and with a few more the electroencephalogram (EEG) showed the slow waves and spikes characteristic of a seizure. Extensive clinical experiences and 4 well-documented controlled trials comparing flurothyl with ECT reported that from 3 to 10 inhalations over a few weeks successfully relieved severe depression and psychosis. In 1957, an alternative seizure-inducing agent, flurothyl (Indoklon), a congener of the inhalant anesthetic diethyl ether, was tested. With a few inhalations consciousness was lost, and with a few more the electroencephalogram (EEG) showed the slow waves and spikes characteristic of a seizure. Extensive clinical experiences and 4 well-documented controlled trials comparing flurothyl with ECT reported that from 3 to 10 inhalations over a few weeks successfully relieved severe depression and psychosis. In 1957, an alternative seizure-inducing agent, flurothyl (Indoklon), a congener of the inhalant anesthetic diethyl ether, was tested. With a few inhalations consciousness was lost, and with a few more the electroencephalogram (EEG) showed the slow waves and spikes characteristic of a seizure. Extensive clinical experiences and 4 well-documented controlled trials comparing flurothyl with ECT reported that from 3 to 10 inhalations over a few weeks successfully relieved severe depression and psychosis.

Durations of the EEG seizure were longer and the effects on cognition and memory were less with flurothyl than with ECT. Motor movements accompanied the EEG seizures, and as in modified ECT, they were readily blocked by pretreatment with succinylcholine. Neither spontaneous tardive seizures nor missed treatments were reported. Pharmacological studies found no systemic toxicity. Yet, flurothyl infusions were discarded, not because of inefficacy or adverse effects but because of fears among clinicians who administered the therapy and breathed the exhaled anesthetic that gave the treatment room a characteristic pungent ethereal aroma. The discarding of this treatment, with its relative lack of adverse effects and considerable benefit, was an error.

The most effective treatment for medication-resistant mood disorders today is ECT; the principal deterrent to its use is the widespread fear of loss of memories. To be sure, in the flurothyl and ECT trials, mild and transitory cognitive impairment was noted during the acute phase. With flurothyl, however, the therapeutic effects were greater, observed earlier, and persisted longer than with ECT. In addition, flurothyl avoided the direct effects of electricity on brain function above and beyond the...
seizure.
Many efforts have been made to reduce the impact of electric currents on brain function. The form of the current, dosing, placements of electrodes, frequency of seizures, and replacement of electricity by magnetic currents have occupied clinicians and researchers for decades. Progress has been made, but public fears have not been allayed. Flurothyl is a unique and rapidly effective anesthetic that has a favorable therapeutic balance. Safe air handling of inhalant anesthetics has been resolved and the fears that inhibited the use of flurothyl are no longer an issue. Seizure management, and control of motor effects and systemic cardiac risks are no longer deterrents to seizure induction with flurothyl.
Much has been learned about the neuroendocrine abnormalities in hypothalamic, pituitary, adrenal, and thyroid functions that accompany mood disorders. Each seizure elicits an outpouring of endocrine peptides. With repeated seizures, the hormone irregularities are redressed and the abnormal mood syndrome relieved. The mechanism of the relief is not known, but the effect is extensively documented.
A reexamination of flurothyl infusions holds promise for improved resolution of severe mood disorders, as well as for a greater understanding of the mechanism of their pathophysiology. A reassessment of the flurothyl experience using present-day anesthesia facilities is encouraged. Acknowledgement—We are indebted to Kathryn Cooper, BS, Class of 2016 of the University of Rochester School of Medicine in New York for a detailed review of the clinical experience with chemical inductions of seizures in man.

Disclosures:
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