Psychiatric Side Effects of Chloroquine

To the Editor: There is considerable interest in the use of chloroquine and hydroxychloroquine for treatment and prevention of coronavirus disease 2019 (COVID-19). Whereas contradictory results have been reported about their efficacy against COVID-19, potentially serious adverse effects, such as cardiac, kidney, liver, and ophthalmologic effects, have been reported.[1]

This letter will emphasize additional potentially serious psychiatric side effects that may be induced by chloroquine. Indeed, in a recent study[2] based on data from the FDA Adverse Event Reporting System database, there were 4,336 adverse event cases following the use of chloroquine, of which 520 (12.0%) reported neuropsychiatric adverse events. Exposure to chloroquine was associated with high reporting of amnesia, delirium, hallucinations, depression, and loss of consciousness but somewhat surprisingly not with suicide, psychosis, confusion, or agitation.

However, the incidence of these and other psychiatric adverse effects with the use of chloroquine is unclear in the absence of high-quality, randomized placebo-controlled trials of its safety. In prophylaxis of malaria, whereas the frequency of serious adverse effects was rare (1/13,600),[3] insomnia and depression were more common, reported in, respectively, 4.5% and 1.4% of individuals at 300 mg/wk (n = 3,827) and 5% and 1% at 600 mg/wk (n = 48,970).[3]

These rates may be comparable to the rates of these effects observed with the use of mefloquine,[4] as early randomized studies that used chloroquine as a comparator revealed approximately similar rates of insomnia and abnormal dreams between drugs.[5,6]

In curative treatment of malaria and in use as an anti-inflammatory drug for lupus erythematosus and rheumatoid arthritis, most of the literature regarding psychiatric adverse effects of chloroquine is based on case reports or case series reporting symptoms such as depression, anxiety, agitation, outbursts of violence, and suicidal ideation, as well as symptoms of psychosis including hallucinations, paranoia, and persecutory delusions.[7] In contrast to many other psychoses, chloroquine-induced psychosis may be more affective and include prominent visual hallucinations, symptoms of derealization, and disorders of thought, but with preserved insight.[8]

Chloroquine-induced psychiatric symptoms can occur in patients with no familial predisposition or personal mental disorders.[8] The frequency of these symptoms does not seem to be related to the cumulative dose or to the duration of treatment.[8] However, the onset of psychosis and other potentially serious effects is usually sudden, and while this typically occurs during the early days to weeks of treatment, there may be delayed recognition of more subtle psychiatric symptoms, which may persist even after stopping the drug. While such persistence has been attributed to chloroquine's extremely long half-life (10–30 days), long-term psychiatric effects extending beyond the drug's persistence in the body cannot be excluded.[4] Of note is that severe COVID-19 has been associated with reports of sleep disturbance, anxiety, agitation, depression, cognitive impairment, and symptoms of psychosis,[9] since these symptoms may resemble those caused by chloroquine and may potentially confound causal attribution.

Thus, the public should be better informed about the psychiatric risks of chloroquine. Considering the poor risk/benefit ratio of chloroquine and hydroxychloroquine, and taking into account the fact that their use for COVID-19 may impact their availability for disorders for which they are known to alleviate symptoms and improve quality of life or course of illness, the FDA revoked on June 15, 2020, the emergency use authorization of chloroquine and hydroxychloroquine for the treatment of COVID-19.

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