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CASE REPORT

Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy

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Key Clinical Message

Susceptibility to quinoline antimalarial intoxication may reflect individual genetic and drug-induced variation in neuropharmacokinetics. In this report, we describe a case of chloroquine intoxication that appeared to be prolonged by subsequent use of multiple psychotropic medications. This case highlights important new considerations for the management of quinoline antimalarial intoxication.

Keywords

Chloroquine, chronic effects, CYP2D6, genetic polymorphisms, pharmacogenetics, psychosis, quinoline.

Introduction

Currently available synthetic quinoline antimalarials, including chloroquine, exhibit idiosyncratic neuropsychiatric effects when administered at low doses used for chemoprophylaxis. Idiosyncratic cases of acute intoxication from quinoline antimalarials have been well characterized in the literature since the first widespread use of the now-outmoded synthetic quinoline quinacrine (also known as atabrine) in the mid-1940s [1, 2]. With subsequent widespread use of chloroquine, a drug developed as a less toxic replacement for quinacrine [3], similar idiosyncratic cases of intoxication [4–6] were soon reported. More recently, similar intoxicating effects from mefloquine, itself developed as a replacement for chloroquine [7], have become well characterized in the literature [8]. Although the naturally occurring quinoline antimalarials have traditionally been considered free of such effects, cases of a related syndrome of intoxication have also occasionally been reported after relatively low doses of quinine [9, 10] and quinidine [11, 12], suggesting a common intoxicating class effect.

Descriptions of chloroquine intoxication in the literature, commonly characterized as toxic psychosis, are similar to those associated with other quinolines and typically feature insomnia [13, 14], mania [15, 16], paranoia and persecutory delusions [17], and auditory and visual hallucinations [18]. Symptoms of intoxication may resemble those of brief psychotic disorder but are more likely to include prominent visual hallucinations, anxiety, restlessness, agitation, and derealization [19]. Suicidality is not uncommon reported [20], and reports of completed sui-

cide [21, 22] attest to the potentially life-threatening nature of such intoxication. Other symptoms of intoxication may include impulsivity, over-talkativeness with flight of ideas, unprovoked laughing or crying [20], personality change, grandiosity, depersonalization [6], and delusional misidentification [23].

Occasionally, intoxication may also induce a delirium [24] or encephalopathy whose symptoms may include confusion [25], difficulties with concentration [26], memory loss and amnesia [27], and catatonia [28].

Although theories have been proposed to explain quinoline intoxication [29, 30], the precise pathophysiological basis of these effects remain unclear despite numerous molecular mechanisms having been identified experimentally. Antimalarial quinolines typically cross the blood–brain barrier to concentrate within the central nervous system (CNS) [31], where many have been demonstrated to directly affect chemical synaptic communication [32], including at serotonin [32, 33], adenosine [34], gamma-amino butyric acid (GABA) [35], and opioid [36] receptors. Various quinolines have also been identified as potent inhibitors of interneuronal electrical communication [37] and are suspected of disrupting transmission between networks of GABA inhibitory interneurons [38, 39]. Such drug-induced inhibitory dysfunction may be sufficient to induce a toxic encephalopathy that mimics in particular the limbic effects of anti-N-methyl-D-aspartate receptor (NMDA) receptor hypofunction [40].

As with other causes of intoxication delirium [41], which may induce neurological abnormalities [24], chloroquine intoxication has been associated with certain extrapyramidal-like movement disorders including stereotypical repetitive movements [42], ataxia [43], facial dystonia and torticollis [44, 45], dysphonias [45], oculogyric dystonia [46], and other neurological effects [47] including tinnitus, vestibulopathy, and accommodative dysfunction [48]. While many symptoms of quinoline intoxication delirium are seemingly reversible with elimination of the drug, use of various quinolines has also been associated with the development of chronic neurological disorders including temporal lobe epilepsy [49], dysautonomia [50], and central vestibulopathy [40]. In addition to reflecting the direct sequelae of encephalopathy, drug-induced brain and brainstem neurotoxicity may underlie at least some prolonged neuropsychiatric effects [51]. For example, in animal models many drugs of the class induce highly focal neurotoxic lesions throughout multiple brain and brainstem areas including the medulla, pons, striatum, and limbic system [51]. Chloroquine may also induce histopathological alterations within multiple neuron subtypes in CNS including within the brainstem and limbic system [52, 53]. In this regard, similarities in the chronic neuropsychiatric sequelae from the antimalarial quinolines shared to a degree with the effects of even the minimally substituted antiparasitic quinoline clioquinol [49, 54] may suggest either neurotoxicity from an as-yet uncharacterized common metabolite, or a direct dose-dependent neurotoxic effect shared among drugs of the class.

Similarly, as neuropsychiatric effects that occur with low doses of quinoline antimalarials during chemoprophylaxis mimic effects more reliably produced at higher doses or dose rates with use in treatment, susceptibility to intoxication and subsequent neurotoxicity during chemoprophylaxis may reflect multifactorial genetic and drug-induced variations in neuropharmacokinetics which may serve to locally increase such metabolite or drug concentrations in brain [51] despite normal serum levels.

In this report, we describe a case of quinoline intoxication that developed while taking low dose chloroquine as chemoprophylaxis that was further exacerbated by the addition of various psychotropic agents used to manage neurobehavioral symptoms associated with the acute intoxication. Pharmacogenetic testing was consistent with absent enzymatic activity of cytochrome P450 (CYP) 2D6, as well as potentially altered activities of CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, and P-glycoprotein (P-gp, or ABCB1). In this report, the possible role of these polymorphisms in contributing to susceptibility to chloroquine intoxication, as well as in prolonging its neuropsychiatric sequelae in the context of psychotropic polypharmacy are discussed together with new considerations for appropriate clinical management of this condition.

Case History

While volunteering in Honduras, a 16-year-old female with an unremarkable medical history became ill during her ninth week of chloroquine prophylaxis (250 mg weekly). She had begun malaria prophylaxis 2 weeks prior to travel, and by her seventh week in Honduras had developed insomnia, paranoia, and confusion that progressed in severity over the next 2 days. Following a dose of diphenhydramine to aid sleep, her symptoms progressed to include hallucinations, irrational guilt and self-persecution, suicidal ideation, and catatonic features. She was taken to a local neurologist where initial workup revealed a normal head CT, unremarkable lumbar puncture, normal complete blood count, negative infectious disease studies, and negative urine toxicology screen.

Upon repatriation to the United States 2 days later, she was admitted to the emergency room of a local hospital where olanzapine and lorazepam were administered for acute management of behavioral symptoms. Upon hospital admission, risperidone and fluoxetine were initiated with lorazepam continued on an as-needed basis for anxiety. On

the second day, benztropine was added while lorazepam was replaced with clonazepam. Her mental status improved briefly by the evening of the second hospital day and she was able to converse with her family and recall many of her experiences over the prior week. However, by the morning of the third day, she had slipped back into a state of marked confusion, self-persecution, paranoia, suicidal ideation, visual and auditory hallucinations, delusional thinking, and catatonia. These progressed in a waxing and waning manner over the next 14 days.

Differential Diagnosis, Investigations, and Treatment

Although chloroquine intoxication was considered in the differential diagnosis, owing to the severity of symptoms and their similarity to those of NMDA receptor (NMDAR) encephalitis [55], cerebrospinal fluid (CSF) collected in Honduras was sent for NMDAR antibody titers, but these were found to be negative. Two additional lumbar punctures were performed over the course of the first 17 hospital days, but these repeat NMDAR antibody titers were also negative. As an additional precaution, an abdominal ultrasound was performed which ruled out ovarian tumors often found in NMDAR encephalitis [56]. CSF samples from each of these collections were also sent to the California Encephalitis Project [57] for additional viral studies but were also negative. A head MRI was normal. A video-EEG was attempted but the patient would not cooperate. Beta-human chorionic gonadotropin (β-HCG) was negative, serum copper was normal, and serum porphyrins were low. Urine toxicology, porphyrins, and heavy metals were all normal. Infectious disease studies revealed a positive serum IgM but negative IgG for *Brucella* and a positive serum IgM for *Mycoplasma pneumoniae*, for which she was treated with a standard dose of azithromycin daily for 5 days. Rheumatologic disease studies were remarkable for a mild elevation in erythrocyte sedimentation rate and thyroglobulin antibody, but normal C-reactive protein. A neurologic exam on hospital day 17 revealed extreme mydriasis, amaurosis, patellar areflexia, dysphonia, and facial palsies.

Despite worsening neurological findings and mental status, the absence of evidence of a treatable organic cause and the need to manage continued symptoms led to transfer to a psychiatric hospital 3 days later. At the time of transfer, she exhibited near-catatonic features. The following day, risperidone, benztropine, and fluoxetine were replaced with olanzapine and lorazepam. Over the next 3 days, she improved remarkably. However, after the fourth day she progressively declined with increasing visual illusions, extreme paranoia with magical and delusional thoughts (e.g., each of the staff were interpreted as celebrities, and she believed a bird outside the window was videotaping her and that she was imprisoned in a foreign country), suicidal ideation and anxiety. She demonstrated a return of facial palsies and abnormal phonation as her dose of olanzapine was increased from 2.5 mg to 17.5 mg daily. The correlation of medication dosage with symptom severity raised suspicion for an exacerbation of toxicity from psychotropic polypharmacy. By hospital day 58, olanzapine was tapered off, after which she rapidly improved and was discharged on hospital day 66 on a single tapering dose of lorazepam only. Outpatient neuro-ophthalmologic exam revealed findings of extreme mydriasis, despite the patient not having been on an anticholinergic medication for over 45 days. This led to suspicion that abnormal medication metabolism was contributing to central anticholinergic toxicity.

Pharmacogenetic testing was then obtained using the Drug Metabolizing Enzymes and Transporters (DMET) DNA Microarray GeneChip® [58], with selected polymorphisms confirmed by direct analysis at the Mayo Clinic Laboratories. Results (Table 1) were consistent with absent CYP2D6 activity [59], and potentially altered CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, and ABCB1 activities. Samples of urine, serum, and CSF that were stored over the course of hospitalization at the California Encephalitis Project were later retrieved and analyzed for the presence of chloroquine and its metabolite. Their presence was confirmed and concentrations of chloroquine in serum were found to be within the expected range [60].

Outcome and Follow-up

The patient convalesced at home off all medications over the next 4 months. She underwent extensive neuropsy-

Table 1. Selected Positive Cytochrome P450 (CYP) and ATP-binding cassette (ABC) Single Nucleotide Polymorphisms (SNP).

Gene	SNP	Reference SNP (rs) ID	Observed Alleles	Notes
ABCB1	-25G>T	rs2235015	T/T	1
	24G>A	rs2235040	A/A	1
CYP1A1	2452C>A	rs1799814	C/A	1
CYP1A2	-163C>A	rs762551	A/A	1,2
CYP2C8	30411A>G	rs10509681	A/G	1
CYP2C9	430C>T	rs1799853	C/T	2
CYP2C19	2608C>T	rs10509681	C/T	1
	-806C>T	rs12248560	C/T	1,2
CYP2D6	1846G>A	rs3892097	A/A	1,2
	100C>T	rs1065852	T/T	1,2
	1661G>C	rs1058164	C/C	1
	4180G>C	rs1135840	C/C	1

1. From DMET DNA Microarray GeneChip®.
2. From direct polymorphism analysis.

chological testing but no localizing deficits could be identified. She then returned to high school where she was noted by family and friends to have experienced further behavioral changes (e.g., baseline introversion gave way to extroversion with excessive use of cellphone and social media and attention-seeking behavior), attention deficit-like symptoms (e.g., diminished attention, concentration) and uncharacteristic learning deficits. During her final exams, she decompensated in apparent exhaustion. Thereafter, she began to demonstrate increasingly bizarre behavior including: periods of catatonic-like features (e.g., often sitting for hours and staring at herself in the mirror), punctuated by hysterical fits of inappropriate laughter. She exhibited ritualistic semiconscious behavior that seemed to appear each evening, with associated insomnia. She reported vague but intense pains in the throat and genitalia. Workups aimed at identifying organic causes of these pains were negative. Attempts at providing an ideal environment for her to rest and sleep failed as her insomnia and declining behavior progressed.

The patient's prolonged neuropsychiatric symptoms were suspected to represent sequelae of chloroquine intoxication encephalopathy. Specialists in quinoline toxicity and psychopharmacology were consulted, and in addition to limbic encephalitis, suspicion of quinoline-induced limbic [49], and brainstem [8] neurotoxicity with possible associated epilepsy or nonconvulsive status epilepticus [61] and neuralgias were also raised. Certain organic causes were again ruled out following a repeat MRI and lumbar puncture that were normal, and CSF sent for a broad panel of midbrain receptor autoantibody titers returning negative. A 48-hour, continuous video-EEG monitoring was also negative for cortical seizures.

Guided by the newly obtained pharmacogenetic testing, a new medication regimen directed at managing her neuropsychiatric symptoms and central cholinergic hypoactivity, and to empirically manage a possible occult seizure disorder was designed. To these effects, valproic acid, paliperidone, and rivastigmine were sequentially initiated. On the third day of valproic acid, an abrupt improvement in mental status occurred whereby the bizarre behavior subsided and the patient was able to engage in detailed conversations on a wide range of topics. The sequential additions of paliperidone followed by transdermal rivastigmine appeared to add small incremental improvements in her cognition, mental status, and behavior. None of these medications initially appeared to lead to any adverse effects.

After a few weeks, the patient's behavior had significantly improved and she was weaned off paliperidone. After a few months, she was weaned off valproic acid while continuing on transdermal rivastigmine only. She convalesced at home for 4 months and returned to finish high school without any behavioral issues but with emerging symptoms of extreme fatiguability, orthostatic intolerance, and attentional deficit all suggestive of the autonomic dysfunction following brain injury [62]. Concerns for rivastigmine contributing to these lingering symptoms led to its substitution with a subsequent gradual taper of an oral formulation that continued through the end of reported follow-up, 36 months after the initial intoxication.

Discussion

While this patient's initial symptoms were remarkably consistent with those in other reports of quinoline intoxication and specifically in prior reports of chloroquine intoxication [6, 14, 15, 17, 20, 25, 42, 63], the extended nature of certain neuropsychiatric effects has not previously been reported with this drug. In this case, pharmacogenetic testing revealed evidence of absent CYP2D6 activity, alterations in the activity of at least five other enzymes including CYP1A1, CYP1A2, CYP2C8, CYP2C9, and CYP2C19 involved in the metabolism either of chloroquine or the psychotropic drugs used to manage her symptoms, and evidence of altered P-gp activity. While these pharmacogenetic findings do not provide definitive insight into the etiology of the patient's original intoxication, they do suggest that it may have been a direct effect of an inability to metabolize chloroquine. Likewise, these pharmacogenetic findings may provide pharmacokinetic explanations for the extended duration of at least some of her symptoms. The plausible pharmacogenetic correlates in this case therefore raise important new considerations for the management of quinoline antimalarial intoxication.

Etiology

In this case, the patient exhibited characteristic symptoms of quinoline intoxication, including insomnia, paranoia, and confusion well prior to use of any other psychotropic drugs. This suggests that the etiology of this intoxication could reflect a primary genetic susceptibility to these effects. For example, genetic susceptibility to mefloquine intoxication has been postulated to primarily reflect polymorphisms in ABCB1 [64, 65]. However, although chloroquine is a potent P-gp inhibitor [66], there is yet little direct evidence that the drug is a significant P-gp substrate *in vitro* [66]. Therefore, whatever alteration in activity might be associated with the homozygous variation in ABCB1 (rs2235015 and rs2235040) observed in this case may not have directly contributed to risk of initial intoxication. Conversely, among other enzymes with polymorphisms suggesting altered activity, CYP1A1, CYP1A2, CYP2C8, and CYP2C19 are all believed to be

involved in chloroquine metabolism [67, 68]. Our patient was found to have heterozygous variation in CYP1A1 (rs1799814), CYP2C8 (rs10509681), and CYP2C19 (rs12248560), and homozygous variation in CYP1A2 (rs762551), but the clinical significance of these in the context of chloroquine metabolism is not clear based on existing studies.

The only enzyme in which a well-characterized alteration in activity was identified in our patient was CYP2D6. Although prior reports have suggested that chloroquine is not significantly metabolized *in vitro* by CYP2D6 [67], it is plausible that brain-specific variations in CYP2D6 expression might play a relevant role in the etiology of chloroquine intoxication *in vivo*. Of the major isoforms thus far found responsible for chloroquine metabolism, only CYP2D6 is known to be relatively more expressed than these isoforms in brain relative to liver [69]. Interestingly in this respect, the proportion of subjects who are found to lack CYP2D6 activity [70], typically 10% or fewer, is similar to the proportion of subjects in studies of chloroquine prophylaxis who report prodromal psychiatric symptoms such as depression, irritability, and confusion [71], which may predict risk of more serious intoxication with continued dosing.

In this case, it may be hypothesized that if brain-specific expression of chloroquine-metabolizing CYP isoforms is necessary to mitigate the risk of intoxication, the absence of CYP2D6 activity might in part explain the observed susceptibility. According to this hypothesis, the addition of fluoxetine, a potent CYP2D6 inhibitor [72], administered during the first 20 days of hospitalization, may have potentially further reduced whatever minimal chloroquine metabolic activity may have been initially present in brain tissue.

Whether or not the hypothesis is correct that the absence of CYP2D6 mediated metabolism of chloroquine in brain may have been primarily responsible in this case for the initial intoxication and its extended duration, it is tempting to speculate that the absence of CYP2D6 activity may also have contributed through other mechanisms to the extended duration of illness. CYP2D6 provides a major pathway for the metabolic inactivation of many of the drugs to which the patient was subsequently exposed, including diphenhydramine [73] used to manage initial symptoms of insomnia, as well as the risperidone [74], fluoxetine [75], and benztropine [76] employed during subsequent hospitalization. In the absence of metabolic inactivation, their potential accumulation to toxic levels may have further complicated clinical presentation. For example, among those with absent CYP2D6 activity and treated with risperidone, a case report has described prolonged neurologic side effects including extrapyramidal movement disorders [74], whereas among those treated with fluoxetine, another case report has described prolonged neurologic side effects including incoordination, ataxia, and seizure [75]. Certain of these side effects might have readily confounded the presentation of chloroquine intoxication had they indeed occurred in our patient.

Clinical application

While pharmacogenetic testing allowed the treatment team to recognize the potential contribution of polypharmacy to the patient's original intoxication, this may have remained of little more than academic interest had it not been for the latent relapse necessitating further treatment. Once symptoms returned, an understanding of the potential contributions of pharmacogenetics to the etiology of her illness aided the treatment team in selecting appropriate therapy.

Antiepileptic agents have been successfully employed in the management of multiple neurological sequelae of brainstem [77] and limbic encephalitis, which may serve as a reasonable pathophysiological model for the brain and brainstem injury [8, 51] that may follow quinoline intoxication encephalopathy [40]. With knowledge of the possibility of a nonconvulsive status as causative or contributory to the waxing and waning presentation, valproic acid was chosen to manage symptoms demonstrated by the patient. Other reasons for its selection included its neuroprotective properties [78, 79], and its efficacy in managing agitation and psychotic symptoms associated with acute confusional states [80, 81]. Whether or not this presumed etiology was correct, the patient seemed to have a dramatic response in mental status by the third dose of valproic acid. Unlike certain other antiepileptic agents, valproic acid is not significantly metabolized by CYP2D6 [82], making it a reasonable choice given the absent activity of this enzyme.

Additionally, paliperidone was also selected to manage the patient's psychotic symptomatology, given its lack of associated CYP metabolism, absence of anticholinergic activity, and minimal sedation and extrapyramidal symptoms [83]. Finally, given evidence suggestive of a dysautonomia and central anticholinergic state, rivastigmine [84] was selected in an attempt to enhance central cholinergic activity.

In addition to informing management of individual future cases of intoxication, this case also highlights the important emerging role of pharmacogenetic testing in the routine prescribing of antimalarial quinolines. Recently, metabolism by CYP2D6 has been shown to be necessary in ensuring reliable antimalarial effects from the related antimalarial primaquine [85]. As standard pharmacogenetic testing becomes ever more widely available,

the assessment of CYP2D6 activity may soon help to inform consideration of alternatives to primaquine in the chemoprophylaxis of malaria disease [86]. However, should the increased risk of neuropsychiatric toxicity among those with reduced CYP2D6 activity hypothesized in this case be found to be shared among other quinolines, this would preclude increasing the dosing of these and related drugs [87] as a safe strategy for overcoming reduced antimalarial effects.

Conclusions

This case suggests important new considerations for the appropriate clinical management of quinoline antimalarial intoxication. Given the generally self-limiting nature of most acute symptoms of quinoline intoxication, clinicians managing future cases may wish to avoid psychotropic polypharmacy. This may potentially avoid prolonging the duration of acute symptoms and may reduce the risk of chronic neuropsychiatric sequelae; both of which may be plausibly linked to individual genetic and drug-induced variation in neuropharmacokinetics.

This case also points to a need for quinoline antimalarial drug development, including prelicensing trials assessing safety and efficacy, to be informed by relevant pharmacogenetic testing among enrolled subjects.

Lastly, this case also emphasizes the critical need for those reporting neuropsychiatric adverse events from antimalarial quinolines to include, wherever possible, the results of standard pharmacogenetic testing panels that include the enzymatic pathways plausibly involved in the neuropharmacokinetics of these drugs.

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Conflict of Interest

RLN has been retained as a consultant and expert witness in legal cases involving claims of antimalarial drug toxicity. All other authors report no financial or other conflicts of interest.

References

1. Newell, H. W., and T. Lidz. 1946. The toxicity of atabrine to the central nervous system. Am. J. Psychiatry 102:805–818.
2. Greiber, M. F. 1947. Psychoses associated with the administration of atabrine. Am. J. Psychiatry 104:306–314.
3. Coatney, G. R. 1963. Pitfalls in a discovery: the chronicle of chloroquine. Am. J. Trop. Med. Hyg. 12:121–128.
4. Burrell, Z. L., and A. C. Martinez. 1958. Chloroquine and hydroxychloroquine in the treatment of cardiac arrhythmias. N. Engl. J. Med. 258:798–800.
5. Mustakallio, K. K., T. Putkonen, and T. A. Pihkanen. 1962. Chloroquine psychosis? Lancet 2:1387–1388.
6. Brookes, D. B. 1966. Chloroquine psychosis. Br. Med. J. 1:983.
7. UNDP-World Bank-WHO. 1983. Development of mefloquine as an antimalarial drug. UNDP-World Bank-WHO update. Bull. World Health Organ. 61:169–178.
8. Ritchie, E. C., J. Block, and R. L. Nevin. 2013. Psychiatric side effects of mefloquine: applications to forensic psychiatry. J. Am. Acad. Psychiatry Law. 41:224–235.
9. Verghese, C. 1988. Quinine psychosis. Br. J. Psychiatry 153:575–576.
10. Jerram, T., and N. Greenhalgh. 1988. Quinine psychosis. Br. J. Psychiatry 152:864.
11. Quintanilla, J. 1957. Psychosis due to quinidine intoxication. Am. J. Psychiatry 113:1031–1032.
12. Deleu, D., and E. Schmedding. 1987. Acute psychosis as idiosyncratic reaction to quinidine: report of two cases. Br. Med. J. 294:1001–1002.
13. Reis, J. 1991. Insomnia induced by chloroquine in the treatment of lupus erythematosus disseminatus. Presse Méd. 20:659.
14. Bhatia, M. S. 1996. Chloroquine–induced recurrent psychosis (brief report). Indian J. Med. Sci. 50:302–304.
15. Mustakallio, K. K., T. A. Pihkanen, and T. Putkonen. 1962. Toxic psychosis during chloroquine treatment. Ann. Med. Intern. Fenn. 51:223–228.
16. Bogaczewicz, J., T. Sobów, A. Bogaczewicz, E. Robak, P. Bienkowski, A. Sysa-Jedrzejowska, et al. 2014. Exacerbations of bipolar disorder triggered by chloroquine in systemic lupus erythematosus–a case report. Lupus 23:188–193.
17. Rab, S. M. 1963. Two cases of chloroquine psychosis. Br. Med. J. 1:1275.
18. Sapp, O. L. 1964. Toxic psychosis due to quinacrine and chloroquine. JAMA 187:373–375.
19. Biswas, P. S., D. Sen, and R. Majumdar. 2014. Psychosis following chloroquine ingestion: a 10-year comparative study from a malaria-hyperendemic district of India. Gen. Hosp. Psychiatry 36:181–186.
20. Mohan, D., E. Mohandas, and R. Rajat. 1981. Chloroquine psychosis: a chemical psychosis? J. Natl Med. Assoc. 73:1073–1076.
21. Good, M. I., and R. I. Shader. 1977. Behavioral toxicity and equivocal suicide associated with chloroquine and its derivatives. Am. J. Psychiatry 134:798–801.
22. Jousset, N., C. Rougé-Maillart, A. Turcant, M. Guilleux, A. Le Bouil, and A. Tracqui. 2010. Suicide by skull stab wounds: a case of drug-induced psychosis. Am. J. Forensic Med. Pathol. 31:378–381.

23. Bhatia, M. S., P. K. Singhal, P. Agrawal, and S. C. Malik. 1988. Capgras syndrome in chloroquine induced psychosis. Indian J. Psychiatry 30:311–313.
24. Maldonado, J. R. 2008. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit. Care Clin. 24:657–722.
25. Garg, P., P. Mody, and K. B. Lall. 1990. Toxic psychosis due to chloroquine. Indian J. Pediatr. 57:133–134.
26. Stuiver, P. C., R. J. Ligthelm, and T. J. Goud. 1989. Acute psychosis after mefloquine. Lancet 2:282.
27. Telgt, D. S., A. J. van der Ven, B. Schimmer, H. A. Droogleever-Fortuyn, and R. W. Sauerwein. 2005. Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann. Pharmacother. 39:551–554.
28. Collins, G. B., and M. S. McAllister. 2008. Chloroquine psychosis masquerading as PCP: a case report. J. Psychoactive Drugs 40:211–214.
29. Alisky, J. M., E. L. Chertkova, and K. A. Iczkowski. 2006. Drug interactions and pharmacogenetic reactions are the basis for chloroquine and mefloquine-induced psychosis. Med. Hypotheses 67:1090–1094.
30. Mawson, A. 2013. Mefloquine use, psychosis, and violence: a retinoid toxicity hypothesis. Med. Sci. Monit. 19:579–583.
31. Dow, G. S., E. Milner, I. Bathurst, J. Bhonsle, D. Caridha, S. Gardner, et al. 2011. Central nervous system exposure of next generation quinoline methanols is reduced relative to mefloquine after intravenous dosing in mice. Malar. J. 10:150.
32. Thompson, A. J., M. Lochner, and S. C. Lummis. 2007. The antimalarial drugs quinine, chloroquine and mefloquine are antagonists at 5-HT3 receptors. Br. J. Pharmacol. 151:666–677.
33. Janowsky, A., A. J. Eshleman, R. A. Johnson, K. M. Wolfrum, D. J. Hinrichs, J. Yang, et al. 2014. Mefloquine and psychotomimetics share neurotransmitter receptor and transporter interactions in vitro. Psychopharmacology 231:2771–2783.
34. Weiss, S. M., K. Benwell, I. A. Cliffe, R. J. Gillespie, A. R. Knight, J. Lerpiniere, et al. 2003. Discovery of nonxanthine adenosine A2A receptor antagonists for the treatment of Parkinson's disease. Neurology 61:S101–S106.
35. Thompson, A. J., and S. C. R. Lummis. 2008. Antimalarial drugs inhibit human 5-HT(3) and GABA(A) but not GABA(C) receptors. Br. J. Pharmacol. 153:1686–1696.
36. Liu, L., Y. Katz, R. Weizman, B. Rosenberg, G. W. Pasternak, and M. Gavish. 1991. Interactions of chloroquine with benzodiazepine, gamma-aminobutyric acid and opiate receptors. Biochem. Pharmacol. 41:1534–1536.
37. Cruikshank, S. J., M. Hopperstad, M. Younger, B. W. Connors, D. C. Spray, and M. Srinivas. 2004. Potent block of Cx36 and Cx50 gap junction channels by mefloquine. Proc. Natl Acad. Sci. USA 101:12364–12369.
38. Gajda, Z., Z. Szupera, G. Blazsó, and M. Szente. 2005. Quinine, a blocker of neuronal cx36 channels, suppresses seizure activity in rat neocortex in vivo. Epilepsia 46:1581–1591.
39. Allison, D. W., R. S. Wilcox, K. L. Ellefsen, C. E. Askew, D. M. Hansen, J. D. Wilcox, et al. 2011. Mefloquine effects on ventral tegmental area dopamine and GABA neuron inhibition: a physiologic role for connexin-36 GAP junctions. Synapse 65:804–813.
40. Nevin, R. L. 2012. Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. Travel Med. Infect. Dis. 10:144–151.
41. Maldonado, J. R. 2008. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Crit. Care Clin. 24:789–856.
42. Sahoo, S., M. Kumar, and V. K. Sinha. 2007. Chloroquine-induced recurrent psychosis. Am. J.Ther. 14:406–407.
43. James, R. F. 2013. Cerebellar ataxia in patients with malaria treated with chloroquine. Postgrad. Med. J. 64:167.
44. Busari, O. A., J. Fadare, S. Agboola, O. Gabriel, O. Elegbede, and Y. Oladosu. 2013. Chloroquine-induced acute dystonic reactions after a standard therapeutic dose for uncomplicated malaria. Sultan Qaboos Univ. Med. J. 13:E476–E478.
45. Singhi, S., P. Singhi, and M. Singh. 1977. Chloroquine-induced involuntary movements. Br. Med. J. 2:520.
46. Singhi, S., P. Singhi, and M. Singh. 1979. Extrapyramidal syndrome following chloroquine therapy. Indian J. Pediatr. 46:58–60.
47. Wittes, R. 1987. Adverse reactions to chloroquine and amodiaquine as used for malaria prophylaxis: a review of the literature. Can. Fam. Physician 33:2644–2649.
48. Scherbel, A. L., J. W. Harrison, and M. Atdijan. 1958. Further observations on the use of 4-aminoquinoline compounds in patients with rheumatoid arthritis or related diseases. Cleve. Clin. Q. 25:95–111.
49. Ferrier, T. M., A. C. Schwieger, and M. J. Eadie. 1987. Delayed onset of partial epilepsy of temporal lobe origin following acute clioquinol encephalopathy. J. Neurol. Neurosurg. Psychiatry 50:93–95.
50. Craige, B., L. Eichelberger, R. Jones, A. Alving, T. N. Pullman, and C. M. Whorton. 1948. The toxicity of large doses of pentaquine (SN-13,276), A new antimalarial drug. J. Clin. Invest. 27:17–24.
51. Nevin, R. L. 2014. Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine. Int. J. Parasitol. Drugs Drug Resist. 4:118–125.
52. Klinghardt, G. W., P. Fredman, and L. Svennerholm. 1981. Chloroquine intoxication induces ganglioside storage in nervous tissue: a chemical and histopathological study of brain, spinal cord, dorsal root ganglia, and retina in the miniature pig. J. Neurochem. 37:897–908.

53. Klinghardt, G. W. 1978. Experimental neuropathology and clinical neurology of chloroquine side effects. Int. J. Neurol. 11:331–341.
54. Konishi, T., K. Hayashi, M. Hayashi, S. Ueno, S. Yoshida, H. Fujimura, et al. 2008. Depression in patients with subacute myelo-optico-neuropathy (SMON). Intern. Med. 47:2127–2131.
55. Dalmau, J., A. J. Gleichman, E. G. Hughes, J. E. Rossi, X. Peng, M. Lai, et al. 2008. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 7:1091–1098.
56. Peery, H. E., G. S. Day, S. Dunn, M. J. Fritzler, H. Prüss, C. De Souza, et al. 2012. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun. Rev. 11:863–872.
57. Gable, M. S., H. Sheriff, J. Dalmau, D. H. Tilley, and C. A. Glaser. 2012. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin. Infect. Dis. 54:899–904.
58. Burmester, J. K., M. Sedova, M. H. Shapero, and E. Mansfield. 2010. DMET microarray technology for pharmacogenomics-based personalized medicine. Methods Mol. Biol. 632:99–124.
59. Zhou, S. F. 2009. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin. Pharmacokinet. 48:761–804.
60. Brohult, J., L. Rombo, V. Sirleaf, and E. Bengtsson. 1979. The concentration of chloroquine in serum during short and long term malaria prophylaxis with standard and "double" dosage in non-immunes: clinical implications. Ann. Trop. Med. Parasitol. 73:401–405.
61. Kaplan, P. W., A. O. Rossetti, E. H. Kaplan, and H. Wieser. 2012. Proposition: limbic encephalitis may represent limbic status epilepticus. A review of clinical and EEG characteristics. Epilepsy Behav. 24:1–6.
62. Kanjwal, K., B. Karabin, Y. Kanjwal, and B. P. Grubb. 2010. Autonomic dysfunction presenting as postural tachycardia syndrome following traumatic brain injury. Cardiol. J. 17:482–487.
63. Good, M. I., and R. I. Shader. 1982. Lethality and behavioral side effects of chloroquine. J. Clin. Psychopharmacol. 2:40–47.
64. Zaigraykina, N., and I. Potasman. 2010. Polymorphism at the MDR1 locus as a cause of mefloquine-induced psychosis. Harefuah 149:583–584, 620, 619.
65. Aarnoudse, A. L., R. H. van Schaik, J. Dieleman, M. Molokhia, M. M. van Riemsdijk, R. J. Ligthelm, et al. 2006. MDR1 gene polymorphisms are associated with neuropsychiatric adverse effects of mefloquine. Clin. Pharmacol. Ther. 80:367–374.
66. Hayeshi, R., C. Masimirembwa, S. Mukanganyama, and A. L. Ungell. 2006. The potential inhibitory effect of antiparasitic drugs and natural products on P-glycoprotein mediated efflux. Eur. J. Pharm. Sci. 29:70–81.
67. Projean, D., B. Baune, R. Farinotti, J. Flinois, P. Beaune, A. Taburet, et al. 2003. In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation. Drug Metab. Dispos. 31:748–754.
68. Kim, K. A., J. Y. Park, J. S. Lee, and S. Lim. 2003. Cytochrome P450 2C8 and CYP3A4/5 are involved in chloroquine metabolism in human liver microsomes. Arch. Pharm. Res. 26:631–637.
69. Dutheil, F., S. Dauchy, M. Diry, V. Sazdovitch, O. Cloarec, L. Mellottée, et al. 2009. Xenobiotic-metabolizing enzymes and transporters in the normal human brain: regional and cellular mapping as a basis for putative roles in cerebral function. Drug Metab. Dispos. 37:1528–1538.
70. Wijnen, P. A., R. A. Op den Buijsch, M. Drent, P. M. Kuijpers, C. Neef, A. Bast, et al. 2007. Review article: the prevalence and clinical relevance of cytochrome P450 polymorphisms. Aliment. Pharmacol. Ther. 26(Suppl 2):211–219.
71. Boudreau, E., B. Schuster, J. Sanchez, W. Novakowski, R. Johnson, D. Redmond, et al. 1993. Tolerability of prophylactic Lariam regimens. Trop. Med. Parasitol. 44:257–265.
72. Sager, J. E., J. D. Lutz, R. S. Foti, C. Davis, K. L. Kunze, and N. Isoherranen. 2014. Fluoxetine- and norfluoxetine-mediated complex drug-drug interactions: in vitro to in vivo correlation of effects on CYP2D6, CYP2C19, and CYP3A4. Clin. Pharmacol. Ther. 95:653–662.
73. Akutsu, T., K. Kobayashi, K. Sakurada, H. Ikegaya, T. Furihata, and K. Chiba. 2007. Identification of human cytochrome p450 isozymes involved in diphenhydramine N-demethylation. Drug Metab. Dispos. 35:72–78.
74. Köhnke, M. D., E. U. Griese, D. Stösser, I. Gaertner, and G. Barth. 2002. Cytochrome P450 2D6 deficiency and its clinical relevance in a patient treated with risperidone. Pharmacopsychiatry 35:116–118.
75. Sallee, F. R., C. L. DeVane, and R. E. Ferrell. 2000. Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. J. Child. Adolesc. Psychopharmacol. 10:27–34.
76. Othman, A. A., S. A. Syed, A. H. Newman, and N. D. Eddington. 2007. Transport, metabolism, and in vivo population pharmacokinetics of the chloro benztropine analogs, a class of compounds extensively evaluated in animal models of drug abuse. J. Pharmacol. Exp. Ther. 320:344–353.
77. Alam, A., and N. V. Puri. 2014. Inefficacy of antipsychotics in treatment of delirium and agitation in two cases of bickerstaff brainstem encephalitis. J. Neuropsychiatry Clin. Neurosci. 26:176–178.
78. Monti, B., V. Gatta, F. Piretti, S. S. Raffaelli, M. Virgili, and A. Contestabile. 2010. Valproic acid is neuroprotective

in the rotenone rat model of Parkinson's disease: involvement of alpha-synuclein. Neurotox. Res. 17:130–141.
79. Lai, J. S., C. Zhao, J. J. Warsh, and P. P. Li. 2006. Cytoprotection by lithium and valproate varies between cell types and cellular stresses. Eur. J. Pharmacol. 539:18–26.
80. Bourgeois, J. A., A. K. Koike, J. E. Simmons, S. Telles, and C. Eggleston. 2005. Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. J. Neuropsychiatry Clin. Neurosci. 17:232–238.
81. Epstein, J., C. J. Madiedo, L. Lai, and M. T. Hayes. 2014. Successful treatment of dopamine dysregulation syndrome with valproic acid. J. Neuropsychiatry Clin. Neurosci. 26: E3.
82. Lopez-Garcia, M. A., I. A. Feria-Romero, H. Fernando-Serrano, D. Escalante-Santiago, I. Grijalva, and S. Orozco-Suarez. 2014. Genetic polymorphisms associated with antiepileptic metabolism. Front. Biosci. (Elite Ed.) 6:377–386.
83. Lautenschlager, M., and A. Heinz. 2008. Paliperidone-ER: first atypical antipsychotic with oral extended release formulation. Expert Rev. Neurother. 8:193–200.
84. Noetzli, M., and C. B. Eap. 2013. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin. Pharmacokinet. 52:225–241.
85. Bennett, J. W., B. S. Pybus, A. Yadava, D. Tosh, J. C. Sousa, W. F. McCarthy, et al. 2013. Primaquine failure and cytochrome P-450 2D6 in Plasmodium vivax malaria. N. Engl. J. Med. 369:1381–1382.
86. Deye, G. A., and A. J. Magill. 2014. Primaquine for prophylaxis of malaria: has the CYP sailed? J. Travel Med. 21:67–69.
87. Marcsisin, S. R., J. C. Sousa, G. A. Reichard, D. Caridha, Q. Zeng, N. Roncal, et al. 2014. Tafenoquine and NPC-1161B require CYP 2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds. Malar. J. 13:2.

