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A REVIEW ON MOLECULAR MECHANISMS BEHIND THE NEUROPSYCHIATRIC ADVERSE EFFECTS OF CHLOROQUINE

Muskan R. Sahu[a†], Smruti D. Lonare[a†], Reva A. Salunke[a†] and Hrishikesh N. Gupta[b]*

[a]Government College of Pharmacy, Amravati, Maharashtra-444604, India.
[b]Assistant Professor Government College of Pharmacy, Ratnagiri, Maharashtra-415612, India.

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***Corresponding Author: Hrishikesh N. Gupta**

Assistant Professor Government College of Pharmacy, Ratnagiri, Maharashtra-415612, India.

ABSTRACT

Chloroquine has been used throughout the globe for treatment of malaria and other parasitic infections since its discovery. In the past few decades, chloroquine was discovered to be effective against wide variety of ailments including autoimmune disorders, viral infections and cancer. Consequently, chloroquine had undergone extensive research for its adverse effects. There are many scientific reports evidencing multiple short-term and long-term adverse effects of chloroquine and its analogues. Among these effects, neuropsychiatric consequences of chloroquine result primarily due to lipophilic nature of the drug and complex arrangement and interlinking of neurotransmitter circuitry in brain. Additionally, multifold cellular effects of chloroquine damage the neuronal and extra-neuronal cells in the CNS and periphery. This review summarizes the neuropsychiatric adverse effects of chloroquine and the cellular mechanism behind them. The adverse effects reported in the *Eudravigilance*, an 'European database of suspected adverse drug reaction reports' are taken for reference and analyzed for their occurrence and susceptibility. Finally, all the scattered and scientifically proved cellular mechanisms responsible for the neuropsychiatric effects of chloroquine are collected together to propose a more logical comprehensive cellular mechanism which will help the researchers to develop strategic plan for use and discovery of better analogues of this wonder drug.

KEYWORDS: Chloroquine, Neuropsychiatric adverse effects, Eudravigilance, Antimalarial adverse effects, lysosomotropic agent, p-glycoprotein.

INTRODUCTION

Chloroquine (CQ), a 4-aminoquinoline compound, has rich history as an antimalarial drug.[1,2] In the 17th century, the discovery of quinine from cinchona bark in Peru was a mystery due to limited primary data, especially from *Jesuits* who collaborated with Andean natives.[3] While *Jesuits* learned about cinchona's use for treating chills, its efficacy against malaria-like fevers was unclear. Further, the lack of records regarding use and efficacy of cinchona bark hindered a full understanding about therapeutic scope of this drug. Despite controversies, its therapeutic value gained recognition against malaria. Quinine's structure was unraveled in 1820, leading to discovery of drugs like chloroquine.[4] The investigation of 4-aminoquinolines, including drug CQ was the benchmark in combat against the blood stages of Plasmodium spp. This finding left behind the 8- aminoquinolines like primaquine, that unfortunately led to hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patient.[4–6]

Chloroquine was first synthesized in 1934 by Hans Andersag and his team at Bayer laboratories and was first introduced in clinical practice in 1947 due to its antimalarial therapeutic effects.[7] Chloroquine gained prominence during World War II when it was extensively used by allied forces to combat malaria in soldiers stationed in malaria-endemic regions.[8] Apart from the antimalarial action, CQ showed its effectiveness for the amoebic dysentery.[9] In the following decades, chloroquine became a cornerstone in the global fight against malaria. In 2006, the world health organization (WHO) approved artemisinin containing combination therapies (ACTs) against uncomplicated *Plasmodium falciparum* infection into the National Malaria Control Program (NMCP).[10] However, over the time, an emergence of triple artemisinin-based combination therapy (TACT) has sparked significant interest for drug-resistant strains of *Plasmodium falciparum* malaria. This triple regimen contained a combination of artemether, lumefantrine, amodiaquine and dihydroartemisinin,

piperaquine, mefloquine. This has proven better outcomes for the treatment of drug resistant malaria and led to a shift in antimalarial treatment strategies. TACT, with its demonstrated effectiveness and ability for treatment, came out as a superior choice. The story delves into the historical context, the development of TACT, and its current evidence, emphasizing its impact on global health, safety, and tolerability.[11] Despite its diminished function in current malaria treatment guidelines, CQ remains a subject of research interest. The historical significance of CQ in the combat towards malaria has left a lasting impact on the area of tropical remedy and continues to be part of the broader conversation on infectious disease management.

Although recent reports suggest the broad-spectrum effects of CQ in treating various medical conditions, it is linked with many potential adverse drug reactions affecting vital organs. Rare and reversible adverse effects of CQ have been reported with short-term treatment including gastrointestinal reactions, irritability, skin itching, headache, dizziness and tinnitus, while long-term treatment for rheumatic diseases may result in visual impairments as the most common side effect.[12,13] However, large dosages or administration by parenteral route may cause hypotension, abnormal electrocardiogram, cardiac dysfunction, and cardiac arrest.[14]

These facts advocate the importance of understanding and monitoring these risks when prescribing or using this drug. It is essential for healthcare providers to recognize and address these adverse reactions to optimize patient safety and outcomes while maximizing the therapeutic benefits of CQ. The high risk of neurological and psychiatric complications associated with chloroquine have been established and have left behind the drug in spite of its multi-faceted mechanisms against several microbial and viral strains. CQ, when used for chemoprophylaxis at low doses have been reported to cause neuropsychiatric effects.[15] In this review, the most commonly reported neuropsychiatric adverse effects of CQ along with the possible mechanism are highlighted with the aim to help the healthcare professionals and researchers develop better strategy for optimal utilization of this potential drug.

Chloroquine causes multiple neuropsychiatric effects

The psychiatric effects of antimalarial drugs have been reported since many years, although they rarely occur. Anna Bogaczewicz et.al mentioned many psychiatric adverse effects of chloroquine including lightheadedness, confusion, disorientation, delusion of persecution, and paranoia associated with visual hallucinations progressing to a catatonic state of agitation.[16] Furthermore, some noticeable sings are- confused state, loss of interest, feeling sad, suicidal ideas, a weeping spell, and impaired insight while some may show overactivity, irritability, talkativeness, experiencing racing thoughts, expressing delusions of reference.[17,18] At maximum dosages, individuals with bipolar disorder can experience manic episodes accompanied by psychotic features, as well as feelings of derealization triggered by CQ.[16,19] A systematic study of series of cases was performed and according to those reports neuropsychiatric events such as psychosis, depression, mania, and catatonia were more common with CQ exposure compared to that of hydroxychloroquine (HCQ) which was seen in lower than 5% patients.[20]

The data collected from the *European database of suspected adverse drug reaction reports* (Table S1 and S2) shows that till date a total of 669 cases of neuropsychiatric adverse effects for chloroquine and analogues have been reported accounting to 127 reactions.[21,22] Of these, 19 reactions were observed to appear in more than 10 individuals totaling to 413 cases and representing 61.73% of total reported reactions. Hence the data of these reactions is presented here (Table 1). As per this report, headache was found to be the most common event with 86 cases, of which 14 cases were not recovered and two fatalities were reported. Headache (86) was followed by dizziness (58), seizures (31), peripheral neuropathy (26), syncope (21), hypoaesthesia (20), generalized tonic-clonic seizures (20), coma (18), somnolence (15), paresthesia (14), loss of consciousness (14), neuromyopathy (13), tremor (13), speech disorder (12), amnesia (11), polyneuropathy (11), areflexia (10), disturbance in attention (10) and migraine (10) with decreasing number of cases respectively. Fatality was highest in coma (55%), and recovery was highest in generalized tonic-clonic seizures (70%). Unfortunately, none of the events showed 100% recovery. This data suggests that although chloroquine is useful in many conditions, it exhibit considerable neurological adverse effects that must be noticed while prescribing this potent drug. The data also indicate predominance of adverse effects in females specifically in the age group 18-64.

P-glycoprotein as an important target of CQ

P-glycoprotein is a key channel present on cell membrane responsible for efflux of drug from any cell, thus detoxifying the cell.[23] The efflux pump is responsible for terminating action of many drugs. Alisky et al. described a significant mechanism of p-glycoprotein inhibition of by CQ. P-glycoprotein has an ability of drug removal from the central nervous system. This protein has affinity for CQ. The latter is supposed to bind with the efflux protein and stop its own transport out of the cell. Thus, ultimately the concentration of CQ increases inside cell due to accumulation.[24] Psychotic activities by these mechanisms can be assessed by a physical and family history, any psychological comorbidities and traumatic events happened with a patient.[25] CQ/HCQ exhibit narrow therapeutic ranges, and toxic effects are strongly linked to a single dose of 20 mg/kg. Fatalities have been reported in definite cases with doses of 30 mg/kg of the drug. Specially in critically ill patients those who have potentially altered metabolism as a hepatic and renal impairment, they may

face an increased risk of adverse reactions while using CQ/HCQ.[26]

Neurotransmitters mediate CQ's adverse effects

The large number of CQ-associated neuropsychiatric adverse effects have been reported to be caused by a core mechanism mediated by neurotransmitters. Since neurotransmitters like acetylcholine, dopamine and serotonin play significant roles in perception, cognition and mood pathways, any disturbance in these physiologically vital regulators induce psychiatric symptoms.[27] CQ acts as a muscarinic antagonist, and interactions between CQ and the muscarinic cholinergic system have been documented.[16,28] Contrarily, mefloquine, a CQ analog inhibits acetylcholinesterase (AChE) and disrupts both peripheral and central cholinergic synaptic transmission. This disruption is evidenced by increased miniature endplate potential (MEPP) frequency, amplitude, and duration at the neuromuscular junction, potentially leading to neurotoxicity.[29] Additionally, CQ antagonizes neurotransmitters such as N-methyl-D-aspartate (NMDA), gamma amino butyric acid (GABA), dopamine, and serotonin (5-HT).[16,30,31] On the other hand, prolonged psychosis symptoms like derealization and depersonalization (delusional misidentification or personality change) occur due to high CNS penetration and higher half-life of CQ.[32] The drug accumulates within the CNS, directly impacting the neurotransmitter systems and disrupting GABAergic inhibiting neurons. Such disruption may lead to toxic encephalopathy resembling the limbic effects of NMDA receptor activity.[33] Besides manifesting the consequences of encephalopathy, the study performed on animal model contributing to the neuropsychiatric effects showed more precise involvement of various regions of brain and brainstem such as pons, medulla, striatum and limbic system.[15]

A comprehensive review reported the competitive inhibitory effect of antimalarial quinine and CQ on 5-HT3 receptors, whereas mefloquine primarily demonstrated non-competitive inhibition.[31] The distribution of 5-HT3 receptor subunit (A-E) is present in central and peripheral nervous system including extra-neuronal cells. These receptors are located in different brain areas such as hippocampus, frontal cortex, amygdala, and brain stem.[34] Docking studies explored how these compounds interact with the 5-HT3-binding site, revealing their capacity to engage with the site due to structural similarity with the 5-HT3. The study potentially explained some reported neurological side effects associated with malaria prophylaxis as these antimalarial compounds may impact serotonergic neurotransmission.[35] The serotonin receptor dysfunction is involved in a series of disorders, including nearly every neuropsychiatric domain as sleep and mood disturbance, sexuality, aggression/impulsivity, biological rhythms, memory, learning, and neuronal degeneration.[36]

CQ analogs disrupt calcium homeostasis through inhibition of acetylcholineterase

CQ reduced the rate of firing of spontaneous action potentials by about 40% when applied locally to the cortical neurons. This effect of CQ was attributed to its concentration dependent inhibition of whole cell calcium current, resulting in suppression of neuronal activity.[37] Mefloquine also exhibits its psychotic effect by disrupting neuronal calcium homeostasis. Prolonged cholinergic neurotransmission exhaust calcium stores leading to disturbed calcium (Ca^{2+}) homeostasis, further contributing to neurotoxic effects.[29] AChE inhibition and Ca^{2+} disruption is associated with memory deficits, seizures, and neurodegeneration in hippocampal neurons.[29,37]

CQ: A lysosomotropic agent

CQ being lipid soluble easily enters brain and other regions in the central nervous system. After getting accumulated within brain cells, CQ enters lysosomes and other cell organelles through lipid bilayer readily. Owing to its weakly basic nature, drug gets entrapped within acidic environment of lysosome due to protonation, becoming a lysosomotropic agent.[38] The concentration of CQ gradually increases within lysosome. Ultimately, CQ accumulation in the lysosome neutralize the low pH within the organelle, and inhibit acidic hydrolases that impair organelle maturation. The detergent like action of CQ degrades lysosomal membrane and loss of lysosomal functions.[39,40] Autophagy is compromised by alteration in endoplasmic reticulum stress response through phosphorylation of eukaryotic initiation factor 2α (eIF2α). Phosphorylation of eIF2α is also linked with immunologic cell death.[38,41,42] Additionally, due to the impairment of endo-lysosomal degradative function, the fusion of lysosome with autophagosome gets inhibited, resulting in cessation of autophagy flux which is otherwise one of the important regulatory mechanisms for cell viability.[43] Cellular senescence, neurotoxicity, and the progression of the disease is linked to the continuous activation of microglia cells within brain.[44] The activation of microglia cells surrounding senile plaques, result in heightened production of pro-inflammatory modulators.[44,45]

DISCUSSION

Many studies have revealed the possible and effective uses of chloroquine. The multiple targets of chloroquine make it a potent alternative in many illnesses ranging from protozoal to viral infections and even cancer.

The therapeutic potential of CQ had been explored in the context of other diseases, such as rheumatoid arthritis and certain viral infections.[9] It had been employed for the autoimmune disorders like rheumatic arthritis (RA) and systematic lupus erythematosus (SLE).[46–48] Recently both CQ and HCQ were widely used for viral infections like Herpes simplex Virus type 1, Zika, HIV, MERS-CoV, HCoV-OC43, Chikungunya and Hepatitis C.[49–56] CQ exhibits diverse mechanisms for anti-cancer

properties, such as inhibiting autophagy, TLR9/NF-kB signaling, stabilizing p53 protein, and affecting glutamate dehydrogenase activity.[57,58] It possesses actions including altering endosomal pH, increasing osmotic pressure, improving gene transfection efficiency, and preventing lysosomal enzyme activity.[59] Studies suggest that the required doses for endosomal escape purposes may not be high enough to hinder successful therapy. This makes CQ a multipurpose therapeutic option in cancer treatment, offering for novel solutions against cancer in the future.[60] In *in- vitro* studies, CQ has been found to inhibit the replication of related coronaviruses such as SARS-CoV and HCoV-229E, and more recently, it has demonstrated efficacy in inhibiting the replication of the novel SARS-CoV-2 (COVID-19) virus.[61] The diverse mechanisms displayed by CQ advocate its possible application as an effective antiviral agent for treating COVID-19.

Despite its usefulness in various conditions, the psychiatric adverse effects of CQ had made it a matter of concern worldwide. Various mechanisms had been reported to be responsible for these adverse effects. In the current review those scattered evidences are collected to propose a comprehensive mechanism behind neuropsychiatric effects of CQ (**Figure 1**). First of all, CQ being a lipophilic moiety, gets entry into brain tissue easily, and attacks the first target- p-glycoprotein. By compromising the functioning of p-glycoprotein, CQ inhibits its own efflux from neurons and other brain cells, and ultimately accumulates intracellularly. The excess CQ then enters and gets entrapped in lysosomes owing to its lysosomotropic effects, disrupts lysosomal maturation and function that is essential for the proper functioning of neuron. Autophagy is the process regulated and implemented by lysososmes through which the cells are supposed to groom themselves for better functioning. Disrupting lysososmal function increases the metabolic and other waste burden on the cell adding up to the oxidative stress and resulting in neurotoxicity. Further, CQ has the potential to directly influence the fine tuning of neurotransmitters within neurons that controls the overall behavior and thought process of an individual. Additionally, the calcium homeostasis is also altered by CQ, further deteriorating the cholinergic neurotransmission. These effects work collectively to cause the numerous psychiatric adverse effects of CQ reported across the world.

Conclusion and future perspectives

Chloroquine, being established and effectively used since long time, had been extensively studied and found effective in many ailments including chronic inflammatory conditions, autoimmune disorders, viral infections, and cancer. The multiple mechanisms of chloroquine have also been investigated that makes this drug a wonder molecule in medicine. Despite of its high potential, the adverse effects of the drug are certain and unavoidable, and sometimes may become fatal. The neuropsychiatric disorders of chloroquine are numerous and can be provoked in those patients who already suffer from these disorders or are prone to develop these effects. Therefore, there is need of a systematic approach for determining the exact cause behind occurrence of these effects and developing a screening protocol to identify the non-tolerant individuals before initiating the treatment. Also, through computer-aided drug design, more effective and safer analogues of chloroquine with lesser side effect can be explored.

Disclosure

The authors declare there are no competing interests to declare.

Data availability

The authors confirm that the data supporting this article is available in this article and supplementary materials.

Table S1: Data obtained from *European database of suspected adverse drug reaction reports* (Eudravigilance) representing the gender and age group-wise distribution of reported neuropsychiatric adverse effects of Chloroquine.

Sr No	Reaction	Age group and gender																Total
		Not Specific		0-1 Months		2M -2Years		3-11 years		12- 17 Years		18-64 Years		65-85 Years		More than 85 years		
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
1	Headache	7	8						1	1	2	18	35		13	1		86
2	Dizziness	3	5							3		15	25		7			58
3	Seizure	3	2			1	2	2		1	2	9	9					31
4	Neuropathy peripheral		3									6	11	1	5			26
5	Syncope	1	1					1				2	13		3			21
6	Hypoaesthesia	2	2									8	5		3			20
7	Generalised tonic-clonic seizure		1					1		1	3	6	8					20
8	Coma		2								2	3	9		2			18
9	Somnolence		4			1				1	2	2	4		1			15
10	Paraesthesia	1									1	4	8					14
11	Loss of consciousness		2			1				3		2	6					14
12	Neuromyopathy											2	8		3			13
13	Tremor		1			1	1					5	2		3			13
14	Speech disorder		2					2			1	3	4					12
15	Amnesia		5							1		2	2		1			11
16	Polyneuropathy											3	6		2			11
17	Areflexia										1	2	5		2			10
18	Disturbance in attention		4				1			1	1	3						10
19	Migraine											1	9					10
20	Lethargy					1		2			1	1	4					9
21	Balance disorder		1			1	1					3	2					8
22	Epilepsy		1								1	3	3					8
23	Ataxia		3									3						6
24	Brain oedema					1	1				1	1	2					6
25	Hyporeflexia											1	4		1			6
26	Memory impairment		1									3	2					6
27	Movement disorder	2	2									1	1					6
28	Altered state of conscioussness		1							1			2		1			5

29	Brain injury		1			1					1	2						5
30	Burning sensation												5					5
31	Depressed level of consciousness		1								1	2	1					5
32	Encephalopathy									1	1	2	1					5
33	Neurotoxicity		1									3			1			5
34	Optic neuritis												2	2	1			5
35	Psychomotor hyperactivity		1									3	1					5
36	Sensory loss											3	2					5
37	Unresponsive to stimuli					1	1					1	1		1			5
38	Carpal tunnel syndrome											1	3					4
39	Dysarthria	1										2				1		4
40	Dysstasia	1	1										2					4
41	Guillain-Barre syndrome		2										1		1			4
42	Motor dysfunction									1		1	2					4
43	Paresis											2	2					4
44	Peripheral sensory neuropathy		1								1		1		1			4
45	Aphasia		1										1		1			3
46	Cerebral congestion					1							2					3
47	Cognitive disorder						1					1	1					3
48	Dyskinesia											1	2					3
49	Extrapyramidal disorder											2	1					3
50	Paralysis											1	2					3
51	Presyncope							1				1		1				3
52	Taste disorder											1	2					3
53	Toxic encephalopathy										1		2					3
54	Ageusia		1										1					2
55	Anosognosia											2						2
56	Brain hypoxia										1		1					2
57	Cerebellar ataxia											1			1			2
58	Cerebrovascular accident		2															2
59	Cranial nerve disorder											2						2
60	Demyelinating polyneuropathy												2					2
61	Dysgeusia											1		1				2
62	Dystonia											2						2
63	Facial paralysis										1		1					2
64	Head discomfort		1									1						2

65	Hypertonia											1	1					2
66	Hypotonia										1		1					2
67	Incoherent											2						2
68	Language disorder						1						1					2
69	Myasthenic syndrome											1	1					2
70	Nervous system disorder											1	1					2
71	Paraparesis												1		1			2
72	Quadriparesis														2			2
73	Sensory disturbance											1			1			2
74	Stupor										1		1					2
75	Tongue biting											1	1					2
76	Hypoxic-ischaemic encephalopathy												1					1
77	Anosmia												1					1
78	Aura												1					1
79	Blood brain barrier defect												1					1
80	Brain stem stroke												1					1
81	Central nervous system lesion												1					1
82	Central nervous system vasculitis													1				1
83	Cerebral artery embolism											1						1
84	Cerebral atrophy											1						1
85	Cerebral haemorrhage					1												1
86	Cerebral small vessel ischaemic disease													1				1
87	Clonic convulsion												1					1
88	Convulsions local														1			1
89	Coordination abnormal						1											1
90	Decreased vibratory sense														1			1
91	Dementia											1						1
92	Developmental coordination disorder					1												1
93	Drooling										1							1
94	Dysgraphia						1											1
95	Electric shock sensation										1							1
96	Focal dyscognitive seizures												1					1
97	Frontotemporal dementia											1						1
98	Horner's syndrome											1						1
99	Hyperaesthesia												1					1
100	Hyperreflexia											1						1

101	Hypersomnia									1								1
102	Hypokinesia		1															1
103	Judgement impaired											1						1
104	Leukoencephalopathy													1				1
105	Muscle contractions involuntary												1					1
106	Muscle spasticity											1						1
107	Myoclonus												1					1
108	Nerve degeneration														1			1
109	Neuralgia												1					1
110	Neuromuscular toxicity												1					1
111	Nystagmus											1						1
112	Paresis cranial nerve											1						1
113	Parkinsonism							1										1
114	Partial seizures									1								1
115	Peroneal nerve palsy							1										1
116	Petit mal epilepsy												1					1
117	Psychomotor skills impaired		1															1
118	Quadriplegia											1						1
119	Reflexes abnormal							1										1
120	Repetitive speech											1						1
121	Resting tremor										1							1
122	Restless legs syndrome												1					1
123	Sciatica												1					1
124	Simple partial seizures									1								1
125	Speech disorder developmental						1											1
126	Tonic clonic movements												1					1
127	Tonic convulsion											1						1
Total		**21**	**66**	**0**	**0**	**12**	**12**	**12**	**1**	**18**	**30**	**170**	**256**	**8**	**61**	**2**	**0**	**669**

Table S2: Data obtained from *European database of suspected adverse drug reaction reports* (Eudravigilance) representing the outcome based distribution of reported neuropsychiatric adverse effects of Chloroquine.

Sr No	Reaction	Outcome							
		Number of individuals							
		Fatal	Not Recovered	Not specified	Recovered	Recovering	Unknown	Recovered with sequelae	Total
1	Headache	2	14	2	22	11	34	1	86
2	Dizziness		5	5	22	7	19		58
3	Seizure	2	1	3	10	2	11	2	31
4	Neuropathy peripheral		8	1	5	4	8		26
5	Syncope	1	1	1	9	1	8		21
6	Hypoaesthesia		7	3	5	1	4		20
7	Generalised tonic-clonic seizure	1		2	14	1	2		20
8	Coma	10			3		5		18
9	Somnolence	2	4		5	2	2		15
10	Paraesthesia		1	2	6	2	3		14
11	Loss of consciousness	4			8		2		14
12	Neuromyopathy		1		4	6	1	1	13
13	Tremor	2	2		4	1	4		13
14	Speech disorder	2	1		4	2	3		12
15	Amnesia		5	1	1	1	3		11
16	Polyneuropathy		4			1	4	2	11
17	Areflexia			1	3	6			10
18	Disturbance in attention		7		1	1	1		10
19	Migraine		2			1	7		10
20	Lethargy	3	1		3	1	1		9
21	Balance disorder		2	1	2	1	2		8
22	Epilepsy	2			4		1	1	8
23	Ataxia				4		2		6
24	Brain oedema	5					1		6
25	Hyporeflexia		1	1	1	2	1		6
26	Memory impairment		3		1		2		6
27	Movement disorder		1				5		6
28	Altered state of consciousness	1			1		3		5

29	Brain injury	2	2				1		5
30	Burning sensation			1	2	2			5
31	Depressed level of consciousness	1			2		2		5
32	Encephalopathy	2			2	1			5
33	Neurotoxicity		1		3			1	5
34	Optic neuritis		2	1				2	5
35	Psychomotor hyperactivity		1		3	1			5
36	Sensory loss		3				2		5
37	Unresponsive to stimuli	2			1		2		5
38	Carpal tunnel syndrome		1				3		4
39	Dysarthria				2	2			4
40	Dysstasia				2		2		4
41	Guillain-Barre syndrome						3	1	4
42	Motor dysfunction			1	2	1			4
43	Paresis				2		2		4
44	Peripheral sensory neuropathy		2		1		1		4
45	Aphasia			1	1		1		3
46	Cerebral congestion	3							3
47	Cognitive disorder				1		2		3
48	Dyskinesia				3				3
49	Extrapyramidal disorder			1	2				3
50	Paralysis				1	2			3
51	Presyncope			1	1	1			3
52	Taste disorder				2		1		3
53	Toxic encephalopathy				2	1			3
54	Ageusia						2		2
55	Anosognosia				1	1			2
56	Brain hypoxia	2							2
57	Cerebellar ataxia		2						2
58	Cerebrovascular accident				1		1		2
59	Cranial nerve disorder					2			2
60	Demyelinating polyneuropathy				1	1			2
61	Dysgeusia		1				1		2
62	Dystonia				2				2
63	Facial paralysis				1	1			2
64	Head discomfort		1				1		2

65	Hypertonia				2				2
66	Hypotonia	2							2
67	Incoherent				1	1			2
68	Language disorder		1				1		2
69	Myasthenic syndrome				1	1			2
70	Nervous system disorder	1			1				2
71	Paraparesis		1			1			2
72	Quadriparesis					1	1		2
73	Sensory disturbance				1	1			2
74	Stupor	1			1				2
75	Tongue biting					1	1		2
76	Hypoxic-ischaemic encephalopathy	0			1				1
77	Anosmia						1		1
78	Aura						1		1
79	Blood brain barrier defect						1		1
80	Brain stem stroke	1							1
81	Central nervous system lesion						1		1
82	Central nervous system vasculitis					1			1
83	Cerebral artery embolism				1				1
84	Cerebral atrophy				1				1
85	Cerebral haemorrhage	1							1
86	Cerebral small vessel ischaemic disease					1			1
87	Clonic convulsion						1		1
88	Convulsions local			1					1
89	Coordination abnormal		1						1
90	Decreased vibratory sense					1			1
91	Dementia		1						1
92	Developmental coordination disorder						1		1
93	Drooling	1							1
94	Dysgraphia		1						1
95	Electric shock sensation					1			1
96	Focal dyscognitive seizures				1				1
97	Frontotemporal dementia		1						1
98	Horner's syndrome						1		1
99	Hyperaesthesia					1			1
100	Hyperreflexia				1				1

101	Hypersomnia						1		1
102	Hypokinesia		1						1
103	Judgement impaired					1			1
104	Leukoencephalopathy					1			1
105	Muscle contractions involuntary						1		1
106	Muscle spasticity				1				1
107	Myoclonus				1				1
108	Nerve degeneration					1			1
109	Neuralgia		1						1
110	Neuromuscular toxicity					1			1
111	Nystagmus						1		1
112	Paresis cranial nerve				1				1
113	Parkinsonism				1				1
114	Partial seizures				1				1
115	Peroneal nerve palsy						1		1
116	Petit mal epilepsy						1		1
117	Psychomotor skills impaired						1		1
118	Quadriplegia				1				1
119	Reflexes abnormal				1				1
120	Repetitive speech				1				1
121	Resting tremor				1				1
122	Restless legs syndrome						1		1
123	Sciatica						1		1
124	Simple partial seizures				1				1
125	Speech disorder developmental		1						1
126	Tonic clonic movements	1							1
127	Tonic convulsion				1				1
Total		**57**	**96**	**30**	**206**	**85**	**184**	**11**	**669**

Figure legend

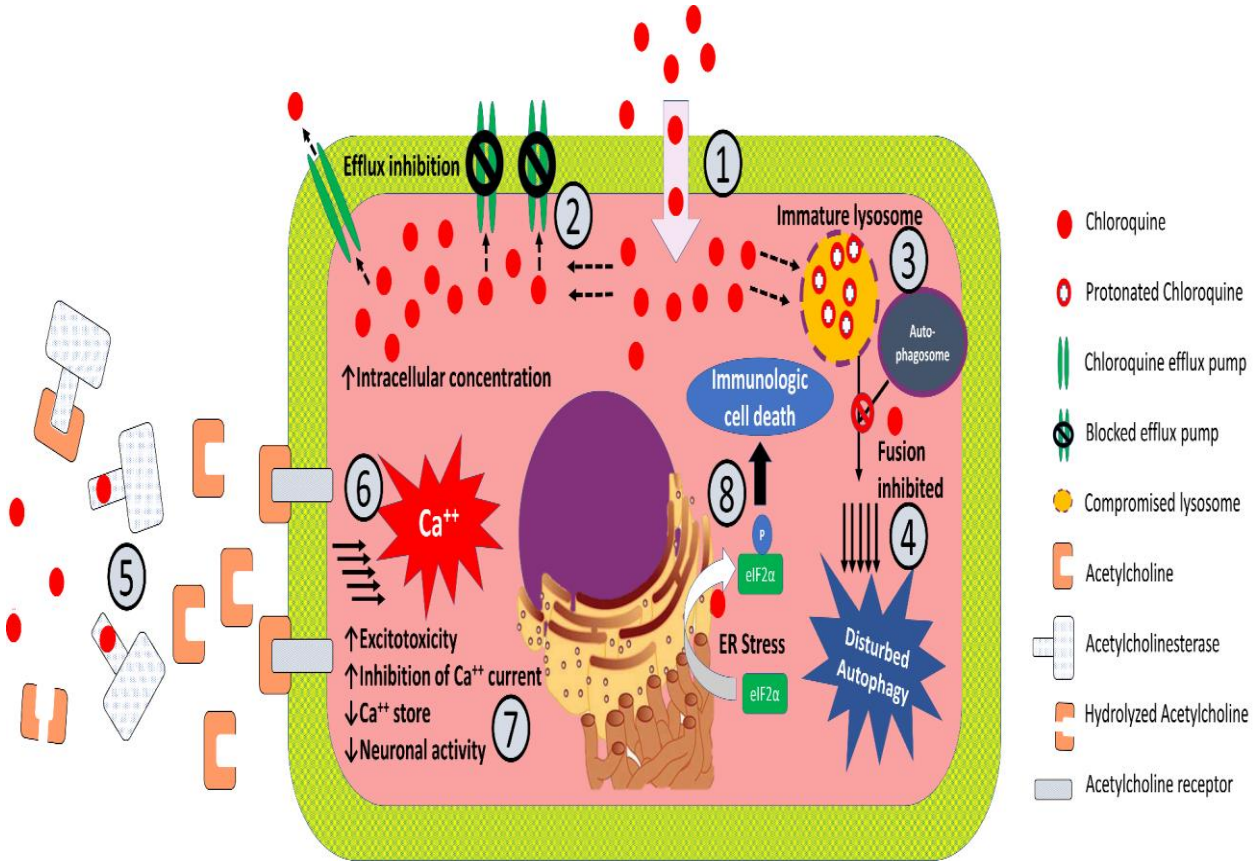

Figure 1: Proposed mechanism of action of CQ for neuropsychiatric effects. 1. Lipophilic nature of CQ allows ready access to CNS., 2. After getting intracellular entry, CQ inhibits the efflux system prohibiting its own exit from the cell, and ultimately, it accumulates intracellularly., 3. The excess CQ then enters and gets entrapped in the lysosomal vesicle, leading to weakening of the lysosomal function., 4. As a result of compromised lysosomal function, the autophagosome cannot fuse with lysosome and the autophagy process is impaired causing increase in metabolic waste., 5. On the other hand enzyme acetylcholinesterase is inhibited, potentiating the cholinergic transmission., 6. Due to excessive stimulation of cholinergic receptors, excitotoxicity and calcium depletion occurs, culminating in 7. reduced neuronal activity., 8. Additionally, CQ induces endoplasmic reticulum induced stress by phosphorylation of eukaryotic initiation factor 2*α*, which may cause immunologic cell death.

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