Drug-Induced Cognitive Impairment

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Abstract

Introduction

Abstract

Drug-induced cognitive impairment (DICI) is a well-established, yet under-recognised, complication of many types of pharmacological treatment. While there is a large body of scientific literature on DICI, most papers are about drug-induced dementia in the elderly and one specific drug class. However, DICI also comprises subclinical symptoms, domain-specific forms of cognitive impairment as well as mild cognitive impairment (MCI), and delirium. Even mild forms of DICI, if not recognised as such, can have deleterious and life-long consequences. In addition, DICI also occurs in younger adults and in children, and has been reported with many different drug classes. The aim of this review is to raise awareness of DICI by providing an overview on the type(s) and symptoms of observed DICI and the suspected underlying mechanism(s) for various drug classes: antiseizure medications, antidepressants, antiparkinsonian drugs, antipsychotics, lithium, benzodiazepines/Z-drugs, opioids, first-generation antihistamines, drugs for urinary incontinence, proton pump inhibitors, glucocorticoids, NSAIDs, statins, antihypertensives, and chemotherapeutic agents.

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Key Points

Many drug classes including non-CNS drugs have a potential to induce various degrees of cognitive impairment, acutely and chronically, and in all age groups.
While there is much research on drug-induced dementia in the elderly, milder forms of drug-induced cognitive impairment (DICI) and DICI in younger populations are less well studied.
Most clinical trials either ignore the cognitive safety of study drugs or use inadequate methods to assess it.
Given the epidemic-like global increase of dementia, more research on DICI is urgently needed.

1 Introduction

1.1 Types and Severity of Drug-Induced Cognitive Impairment

Drug-induced cognitive impairment (DICI) is a term used for a decline in cognitive functions that is primarily caused by medication. It is an unwanted, negative effect on cognitive abilities that can arise from both CNS-active agents and non-CNS-active agents. These negative effects on cognition are mediated by a multitude of pathophysiological mechanisms, as we will show in this paper. The type of cognitive impairment, its course, and its severity may therefore differ between drugs and patients.

DICI can mimic any type of cognitive impairment caused by disease or aging and may therefore be insidious in the sense that it can be interpreted as symptoms and worsening of an existing disease or as onset of a new disease or condition [1]. As we will describe later, DICI may affect functions in only one or in several cognitive domains. Memory problems are a common symptom of DICI and can present as difficulty recalling instructions or recent events or missing important appointments. Confusion or disorientation regarding space and time may occur. DICI affecting functions within the attention domain often present as being distracted and having difficulties focusing on a specific task. Slow thinking and processing speed as well as decreased reaction time and motor slowness are also common symptoms of DICI. Difficulties with language and communication may occur, such as trouble finding the right words, slurred speech, or increased response latency. More elaborated cognitive tasks, such as complex problem-solving, decision making, planning, or organising activities may be affected. With medications that induce sedation, cognitive impairment may occur as a consequence of sleepiness [2].

Often, DICI manifests clinically with acute symptoms such as severe confusion or delirium. Older patients with pre-existing cognitive impairment are at particularly high risk of developing drug-induced delirium [1, 3]. The distinction between delirium and dementia may sometimes be confusing. However, the main distinguishing features of delirium are the acute onset of an impaired level of consciousness, most often accompanied by illusions or hallucinations, changes in perception as well as other acute symptoms that are not typical for dementia [4].

DICI may appear shortly (hours or days) after starting a new drug, but it can appear at any time during treatment, even after long-term use of several years. The degree of cognitive impairment correlates often, but not always, with dose or serum concentration. In most cases, altered cognitive functions normalise after dose reduction or tapering off the drug. Usually, this also applies to the more severe cases such as dementia-like states, as the underlying pathophysiology of drug-induced dementia most often is functional (as opposed to structural). However, there are exceptions to this rule and DICI may persist for months or years if structural changes have developed [5, 6].

DICI severity ranges from subtle, subclinical symptoms to mild cognitive impairment (MCI) and, finally, dementia. MCI involves some deterioration of cognitive function in at least one cognitive domain, combined with subjective complaints or observations by a proxy, with a preserved over-all cognitive functioning. By contrast, dementia is more severe in terms of objective cognitive deficits and includes loss of autonomy in several activities of daily living [7].

Clinical studies, reviews, meta-analyses, and guidelines addressing DICI tend to focus on (a) the elderly, (b) manifest dementia, and (c) drugs with anticholinergic or sedating properties. It is important to note, though, that a wide range of medications can negatively impair cognition—to varying degrees, and in all age groups.

1.2 Epidemiology

Drug-induced dementia has been estimated to account for 2.7–10% of all dementias [1, 8]. A 1988 review of 32 studies found that drugs represent the most common cause of reversible dementia, accounting for 28.2% of the cases [5]. To the best of our knowledge, no newer data are available. However, prescription rates and the individual total drug load have increased in the last decades which means that these numbers could be higher today [9, 10]. The risk of drug-induced dementia increases with polypharmacy: three-fold with two to three drugs, nine-fold with four to five drugs, and 14-fold with more than 6 drugs [11]. The prevalence of polypharmacy (i.e., treatment with five or more drugs) is globally increasing in adults of all age groups, reaching over 60% in people aged 65 years or older in some Western countries [12,13,14]. Clinical experience and case reports suggest that drug-induced dementia is not always recognised as such. In such cases, the cognitive problems may continue for years [15,16,17,18,19,20].

Drugs are one of the most common causes of delirium, especially in the elderly [1, 21]. Medications with anticholinergic and sedating properties are particularly well known for this, but other drug classes can also induce delirium. In elderly, hospitalised patients, drugs have been reported as the cause of delirium in up to 30% of all cases [22]. Polypharmacy more than doubles the risk [23]. Physicians often miss drug-induced delirium which suggests that the true numbers may be even higher [21].

It must be emphasised that the above epidemiological data apply to delirium and dementia. Aside from case studies and reports, there is a lack of epidemiological data and systematic studies on milder, more subtle forms of DICI, and on DICI in younger adults and children.

Recent research suggests that 10–20% of adults aged ≥65 years have MCI [24]. The prevalence of dementia roughly doubles for every 5 years of age [25]. With the world population growing older, an extensive surge in MCI and dementia cases is anticipated. Projections suggest a rise from 57 million dementia cases worldwide in 2019 to 153 million cases by 2050 [26].

Drugs have been identified as a modifiable risk factor for Alzheimer's disease [27]. However, while the World Health Organization states nine factors that increase the risk of developing dementia, drugs are not mentioned [28]. Alzheimer's Disease International counts 12 modifiable risk factors for dementia except drug treatment [29]. Similarly, frequently cited reference texts or position papers do not mention drugs as a possible risk factor for MCI or dementia [26, 30, 31].

1.3 Drug-Induced Cognitive Impairment in Clinical Studies

There is a considerable amount of research on DICI, mainly addressing dementia. However, clinical trials and other studies examining the risk of DICI for certain drug classes often yield conflicting results. The main reasons for this are different study designs and inappropriate methodology, for example, short observation periods and/or the use of screening tools instead of neuropsychological testing. Questionnaires and screening tools like the mini mental state examination (MMSE) or Montreal cognitive assessment (MoCA) have limited sensitivity and specificity. False-positive and, particularly, false-negative results as well as misclassifications are common [32,33,34,35,36,37,38].

In addition, only 6.5% of clinical drug trials actively assess the cognitive safety of the trial drug [39]. Of these few trials, the vast majority uses questionnaires or screening tools, which increases the risk of not detecting milder cognitive impairment, especially in younger or more well-functioning patients. In addition, it is common practice that published safety data from randomised controlled trials (RCTs) do not report adverse events that were observed in less than five percent of the participants. Thus, systematic reviews and meta-analyses using published safety data from RCTs are particularly prone to produce negative results on DICI. This is important to keep in mind when reading this review. Also, study results only apply to the studied population as a whole and, usually, to only one drug or drug class. However, a negative result on the group level does not exclude the possibility of DICI occurring with certain drug combinations, in certain subgroups, or in individual patients.

Another limitation of RCTs is the narrow scope of the populations studied because of strict inclusion and exclusion criteria. This results in a considerably reduced generalisability to the clinical population in real life, which typically exhibits greater comorbidity, greater numbers (and other types) of comedication, and more pronounced fragility [40]. Consequently, patients at higher risk of adverse events may be inadequately represented in RCTs. This may explain why certain adverse drug reactions have a much higher prevalence in real life than in RCTs [41].

From these points, there is reason to suspect that DICI is considerably under-recognised. Therefore, the aim of this review is to increase awareness. Its focus lies in describing the various drug classes' potential to induce cognitive impairment, and (possible) underlying mechanisms.

2 Literature Search Strategy

A comprehensive search strategy using various search strings was employed to identify relevant articles, including case reports, register studies, cross-sectional studies, prospective clinical studies, systematic reviews, and meta-analyses from electronic databases such as PubMed, Google Scholar, and Scopus. Combinations of keywords and phrases related to various drug classes and different forms of cognitive impairment were used to retrieve relevant literature. The search was not limited by publication date, but newer publications were preferred to ensure that this review reflects current knowledge. Additionally, reference lists of relevant articles were reviewed to identify additional sources.

3 Drug-Induced Cognitive Impairment According to Drug Class

An overview of different drug classes, the type of associated cognitive impairment, and possible underlying mechanisms of action is given in Table 1.

Table 1 Overview of drug classes, associated type of cognitive impairment, possible underlying mechanisms, and patient groups at particularly high risk

Full size table >

3.1 Antiseizure Medications

Numerous studies have established that antiseizure medications (ASMs) can impair cognition, even at drug concentrations within the reference range [42,43,44,45]. Polypharmacy and high ASM blood levels increase the risk. However, epilepsy itself is associated with cognitive impairment. Thorough neuropsychological testing may be necessary to distinguish disease-related cognitive symptoms from DICI [46].

Antiseizure medications commonly regarded as having a relatively high risk of cognitive impairment are carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate, topiramate, and zonisamide. They all can impair executive functions, attention, processing speed, learning, and memory [42, 44, 45]. In addition, the latter two ASMs are notorious for their potential to negatively affect speech and verbal memory [47, 48]. This distinguishes topiramate and zonisamide from other ASMs and gives them a specific cognitive profile.

ASMs generally considered as having a small risk of cognitive impairment are gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, and pregabalin [43]. For the most recent ASMs there are insufficient data. It must be noted that 'small risk' does not mean 'no risk' as most often the risk increases with the dose. However, the latter is not always the case. Lamotrigine, for example, is generally regarded as cognitively safe or even beneficial for cognition. However, case reports describe severe aphasia and rapidly progressive dementia-like condition in paediatric and adult patients even at low doses [49, 50]. Also, drugs with a small risk of cognitive impairment may still have a considerable potential to induce a range of other neurologic or psychiatric adverse effects. Levetiracetam, for instance, is not known to impair cognition. However, it is well known for inducing hostility and aggressive behaviour in both children and adults [51].

ASMs affect nerve cell excitation and communication by a large variety of molecular mechanisms. Most block ion channels or bind to various receptors. Two out of three ASMs act by amplifying GABA. Practically all ASMs possess multiple mechanisms of action and the new ASMs share many of their mechanisms with the older ASMs [52, 53]. It is therefore difficult to ascribe their cognitive effects—or lack thereof—to a specific mechanism of action. It is noteworthy, though, that only topiramate, zonisamide, and sulthiame inhibit carbonic anhydrase and all three drugs impair cognition, especially verbal memory [53, 54].

Acute and chronic effects: Usually, symptoms of cognitive impairment by ASMs develop gradually over weeks to months. However, patients may present with various acute cognitive symptoms at any time after treatment initiation, such as considerably reduced executive functions, aphasia, delirium, and even neurological symptoms resembling stroke, especially after rapid dose titration or after substantial dose increases [55,56,57].

Patient groups at high risk: Patients with neurologic or psychiatric comorbidity, pre-existing cognitive impairment, polytherapy, or high ASM serum concentrations (possible even at normal doses if an ASM is combined with an enzyme inhibitor).

3.2 Antidepressants

Depression is associated with reduced cognitive function in several cognitive domains. It can therefore be difficult to distinguish such cognitive impairment from adverse drug effects. While many studies did not find an increased risk of dementia with antidepressant use or even beneficial effects, other studies did [58,59,60,61]. Moreover, as mentioned above, DICI is not only manifest dementia.

Tricyclic antidepressants are well known for their negative impact on cognition. This is usually ascribed to their strong anticholinergic properties. However, tricyclics also have considerable antihistaminergic properties. It is well-known that blocking cerebral histamine receptors, especially the H1-receptor, induces sedation and sleepiness which inevitably impairs attention and cognitive speed. The role of histamine in the pathogenesis and pharmacological treatment of depression has recently gained attention [62]. However, aside from its role in the sleep-wake rhythm, histamine also has an important role in cognitive functioning [63]. Blocking of these receptors by tricyclic antidepressants may therefore contribute to their negative cognitive effects. The American Geriatrics Society recommends that tricyclics (plus paroxetine, a selective serotonin reuptake inhibitor [SSRI] with anticholinergic properties) be avoided in older patients [64].

Non-tricyclic, modern antidepressants have long been regarded as either cognition neutral or cognition improving [65, 66]. However, it is unclear whether the latter is a direct effect. As depression itself is generally associated with impaired cognition, including dementia-like conditions, relieving a person from depression may improve their cognitive problems as well. Moreover, newer research indicates that cognitive impairment is common during treatment with newer antidepressants and that it may resemble adverse drug effects rather than residual symptoms of depression [67,68,69,70,71]. This notion is supported by the observation that SSRIs may impair cognitive function even in healthy subjects [72].

Modern antidepressants may induce cognitive impairment by various mechanisms. Practically all classes of antidepressants, including tricyclics, commonly induce hyponatraemia, a condition that leads to various neurological symptoms including confusion, cognitive impairment and delirium [73,74,75].

Paroxetine, an SSRI, can induce cognitive impairment through its strong anticholinergic properties [64, 76, 77] and deteriorate hippocampal functioning, possibly by induction of excessive neurogenesis in the dentate gyrus which produces cells that behave differently from those cells naturally generated in the dentate gyrus [78].

Noradrenergic and specific serotonergic antidepressants (NaSSAs) like mianserin and mirtazapine are known to produce fatigue and may impair attention, speed and visuospatial ability through their pronounced antihistaminergic properties [79,80,81]. Mianserin produced slowed reaction time and reduced psychomotor function in healthy subjects while mirtazapine may reduce driving ability [82,83,84].

The positive effects of dopamine and norepinephrine on cognition (in patients with ADHD) follow an inverse U-shaped dose–effect curve, meaning that too much stimulation may impair cognition, particularly cognitive flexibility. This has been demonstrated for central stimulants like methylphenidate or amphetamine [85, 86]. Because of their strong pharmacological similarities with central stimulants, it may also apply to noradrenaline and dopamine-enhancing antidepressants, that is, noradrenaline and dopamine reuptake inhibitors (NDRIs) like bupropion as well as serotonin and noradrenaline reuptake inhibitors (SNRIs) like venlafaxine or duloxetine (the latter two drugs also block the reuptake of dopamine) [87,88,89].

Acute and chronic effects: Anticholinergic cognitive effects (mainly memory-related) and antihistaminergic effects (mainly sedation and impaired learning) may manifest within days after start of treatment. Symptoms of dopaminergic/noradrenergic overstimulation in the form of reduced cognitive flexibility may occur within days to weeks. Hyponatraemia, often leading to acute symptoms like confusional state or delirium, may occur at any time after treatment initiation—one study reported a median time to onset of hyponatraemia of 13 days, ranging from 3 to 120 days [90].

Patient groups at high risk: Older adults are particularly susceptible to DICI by antidepressants. Women appear to be at a two to three times higher risk for antidepressant-induced hyponatraemia than men [90, 91].

3.3 Antiparkinsonian Drugs

The loss of dopamine in Parkinson's disease often causes cognitive decline and in some, Parkinson dementia. Without neuropsychological testing, it can be demanding to distinguish disease-related cognitive impairment from DICI [35]. Parkinson's disease is commonly treated with dopaminergic drugs and, sometimes, anticholinergic drugs like trihexyphenidyl, biperiden or benztropine.

The deleterious effects of anticholinergic drugs on cognition are undisputed and reviewed elsewhere in this paper [64, 92].

Dopaminergic drugs comprise L-DOPA, dopamine agonists as well as monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) inhibitors. While there is much focus on psychiatric and behavioural adverse effects of dopaminergic treatment, DICI is less recognised. L-DOPA, unlike common dopamine D2/D3 agonists, can enhance learning, working memory, and executive functions. This has been ascribed to the fact that dopamine binds to both D1 and D2 receptors whereas dopamine agonists mainly bind to D2 and D3 receptors [93]. D1 receptors, involved in phasic dopaminergic stimulation, are crucial for things like working memory and learning. This may explain why L-DOPA has a cognition-improving effect while dopamine agonists do not. To the contrary, several studies suggest that dopamine agonists, either in monotherapy or combined with L-DOPA, might impair cognitive function after a single dose [94,95,96,97,98]. However, both L-DOPA and dopamine agonists can induce confusional or delirious states with fluctuating arousal, impaired attention, and incoherent verbal output, especially in combination with anticholinergic drugs. Frequencies of 5–25% have been reported, and the risk is higher with dopamine agonists than with L-DOPA [22, 99]. Delirium is also common with amantadine or MAO inhibitors [99].

As dopaminergic treatment can induce psychotic and obsessive-compulsive symptoms as well as reduced impulse control, treatment with antipsychotics may become necessary. Among the most used antipsychotics in Parkinson's disease are clozapine and quetiapine, mainly because of their weak antidopaminergic properties. However, clozapine has strong anticholinergic and antihistaminic effects. Quetiapine has weaker anticholinergic effects but has pronounced antihistaminic properties. This may explain the observed impairments in processing speed, verbal memory, and executive functions with these drugs, even at normal doses [100,101,102,103,104,105]. However, these findings possibly do not apply to patients with Parkinson's disease as effective doses and serum concentrations usually are far below those used in schizophrenia and related disorders [106].

Acute and chronic effects: Dopamine agonists may impair cognitive function at any time. Usually, these effects develop gradually over weeks. However, in healthy subjects they were observed after a single therapeutic dose.

Patient groups at high risk: Patients with existing cognitive decline and those with anticholinergic comedication.

3.4 Antipsychotics

Schizophrenia and schizoaffective disorders are associated with a wide range of cognitive impairment which may make it difficult to assess possible negative effects of antipsychotic drug treatment on cognition [107]. In parallel with depression, treating the underlying disease often improves cognitive function, but antipsychotics may also exert detrimental effects on cognition, even at low doses [108].

Antipsychotics bind to a variety of receptors including dopamine, norepinephrine, serotonin, histamine, and muscarinic acetylcholine receptors. Second-generation antipsychotics do so with great variation in affinity, which gives each of these drugs a distinct receptor profile [109].

Typical or first-generation antipsychotics all have strong dopamine D2-antagonistic properties. Dopamine plays an important role in cognition and is involved in, for example, attention, motivation (important for learning and planning), working memory, processing speed, and impulse control [85]. Cognitive adverse effects of typical antipsychotics have been documented in animal models, healthy subjects, and patients with schizophrenia [110]. Chlorpromazine and thioridazine, in addition, have strong anticholinergic and antihistaminergic properties which impair processing speed and memory functions. Other first-generation antipsychotics do not have noteworthy anticholinergic effects.

Atypical or second-generation antipsychotics also block dopamine D2 receptors, although with lower affinity, and some of them only as partial antagonists. They typically bind with varying affinity to different serotonin (5-HT) receptors, thereby modifying dopaminergic neurotransmission [109, 111].

Clozapine, quetiapine (see Sect. 3.3*Antiparkinsonian Drugs*), and olanzapine also have strong anticholinergic properties. This gives them not only the potential to impair cognition, particularly memory functions, but also a potential to induce acute delirium. Olanzapine and quetiapine, in addition, exert strong antihistaminic effects which explains why they are used as sedatives, usually at doses lower than antipsychotic doses. The combination of antidopaminergic and anticholinergic properties, even without antihistaminergic effects, increases the cognitive risk [112,113,114,115]. A retrospective study with over 300,000 patients found that atypical antipsychotics increased the risk of developing Alzheimer's disease by 24% [116].

Aside from their effects on dopaminergic, cholinergic, and histaminergic neurotransmission, antipsychotics may impair cognition by several other mechanisms. Atypical antipsychotics have a demonstrated potential to induce metabolic syndrome. Obesity is associated with impaired insulin regulation, hyperlipidaemia, and vascular damage, factors known to decrease cognitive function [117, 118].

Several studies, among them double-blind, placebo-controlled ones, found significantly reduced cortical thickness after treatment with antipsychotics, especially in the prefrontal cortex [119,120,121,122,123,124]. The underlying mechanisms are unclear. While vascular damage may lead to an undersupply of nutrients and oxygen, some data also point to altered regulation of gene expression (i.e., epigenetic changes) [125]. Interestingly, cortical thinning was positively correlated with higher cumulative intake of typical antipsychotics but less with atypical antipsychotics [126]. This may be caused by the atypical antipsychotics' interference with cholesterol metabolism as cholesterol is essential for the myelination of both white and grey matter [121].

Acute and chronic effects: Acute cognitive impairment due to antihistaminergic effects (mainly sedation and impaired learning) and anticholinergic effects (mainly impaired memory) may occur at any time after start of treatment. Antipsychotics, particularly atypical ones with strong anticholinergic effects, can induce acute delirium. Chronic treatment increases the risk of developing dementia.

Patient groups at high risk: Older adults (due to age-related factors and the prevailing polypharmacy).

3.5 Lithium

Lithium is a chemical element. While there are several hypotheses on how it may exert its therapeutic effects, it is not exactly known by which molecular mechanisms it does so [127]. Adverse effects of lithium are well described in the literature [128]. Regarding cognition, data are conflicting. Many studies found a neuroprotective and cognition-enhancing effect of lithium while other studies and case reports suggest that lithium can impair cognition even at normal plasma concentrations and without other signs of lithium toxicity [127, 129,130,131,132,133,134]. Symptoms are highly variable, acute or chronic, and may include reduced alertness and attention, impaired learning, reduced orientation and visuospatial memory, dysphasia, aphasia, acalculia, confusion, slowed psychomotor function, or acute delirium. If such symptoms manifest despite normal lithium blood levels, an EEG may reveal lithium toxicity [135].

Acute and chronic effects: Acute lithium-induced DICI due to high serum concentration may occur at any time during treatment and is usually accompanied by other neurological symptoms. However, lithium-related DICI despite normal serum concentration and chronic cognitive impairment lasting for months or years has also been reported [133, 134, 136].

Patient groups at high risk: Patients on polytherapy with other CNS-active drugs; older adults and other patients with reduced kidney function including users of NSAIDs.

3.6 Benzodiazepines and Z-Drugs

These drugs amplify physiological GABAergic neurotransmission through modulation of the $GABA_A$ receptor. This induces anxiolytic effects, reduced vigilance and psychomotor abilities, sedation, and sleepiness [137, 138]. It can also induce anterograde amnesia [139, 140]. Such effects may impair various cognitive domains, especially in the elderly [141,142,143]. Dementia-like states have been reported [144,145,146]. Administration of benzodiazepines to older adults hospitalised after major surgery is associated with increased postoperative delirium [147]. Even if only taken at bedtime, the long half-life of common benzodiazepines produces pharmacologically relevant plasma levels during daytime. The American Geriatrics Society recommends for various reasons that these drugs be avoided in the elderly, including the risk of falls [64]. Z-drugs are used as hypnotics, meaning they are only taken at bedtime. They have much shorter half-lives than common benzodiazepines (1–5 h vs 6 to >24 h), and therefore the risk of being cognitively impaired in the daytime is considerably lower [138, 148]. However, the American Geriatrics Society recommends avoiding their use in older patients for the same reasons as benzodiazepines [64].

Acute and chronic effects: In drug-naïve subjects, the cognitive effects of benzodiazepines and Z-hypnotics may manifest after a single dose. Administration of benzodiazepines to hospitalised older adults is associated with a significant risk of delirium. With chronic treatment, most people develop some degree of tolerance. However, chronic treatment may have a cumulative negative effect on cognitive function and is associated with an increased risk of developing dementia [145, 146].

Patient groups at high risk: People with pre-existing cognitive impairment or other neuropsychiatric conditions (all age groups).

3.7 Opioids

Like other neurological and psychiatric conditions, pain itself is associated with impaired cognition, which can make it difficult to identify DICI, especially its milder forms [149]. However, it is well documented that opioids can produce slowed reaction time, reduced psychomotor abilities, reduced attention, disturbed consciousness, confusion, or delirium [36, 150,151,152]. This can occur at normal doses, and even when administered as a patch [153]. These symptoms are often accompanied by psychiatric symptoms such as anxiety or hallucinations. A well-known phenomenon is postoperative confusion or delirium. Many patients who wake up after surgery are confused and disorientated for some time, but reduced verbal recall and impaired arithmetic fluency have also been reported [154]. Opioid use outside clinical settings increases the risk of workplace accidents [155]. Recently, opioid-induced amnestic syndrome has emerged as a complication of opioid abuse. It has mainly been reported with fentanyl and is associated with hippocampal damage, but other cortical and subcortical structures like the basal ganglia or the cerebellum are also often involved [156,157,158].

Opioids exert their pain-relieving effect mainly through binding to opioid receptors in the CNS. These receptors are coupled to inhibitory G-proteins. All three major receptor subtypes (μ, κ, and δ) thus inhibit adenylyl cyclase, thereby disrupting certain intracellular signalling pathways and decreasing intracellular energy levels. In addition, opioids modulate calcium and potassium channels and produce hyperpolarisation which prevents neuronal excitation and propagation of action potentials [159, 160]. Besides binding to opioid receptors and ion channels, opioids also block glutamatergic NMDA receptors and muscarinic acetylcholine receptors [160, 161]. These mechanisms of action may explain their analgesic effect as well as their sedative properties and their negative effects on cognition [162].

Cognitive effects of long-term opioid use are less well studied than acute effects, but there are some experimental and clinical data. For example, several studies have shown that opioids reduce neurogenesis in the hippocampus (for a review, see [163]). Prolonged, but not acute, exposure to morphine may induce neuronal apoptosis [164]. While most clinical studies did not find any effect of opioids on the risk of developing dementia, newer studies, including controlled prospective and paediatric studies, have shown a slightly to considerably increased risk [165,166,167,168]. A large Danish register-based study found that new opioid use in older adults with dementia is associated with a significantly increased risk of death, including an 11-fold increase in the first 2 weeks [169].

Acute and chronic effects: See preceding text.

Patient groups at high risk: Patients with existing cognitive impairment or other neuropsychiatric disorders; patients with concomitant CNS-depressant drugs; older adults.

3.8 First-Generation Antihistamines (Sleeping Aids)

First-generation antihistamines, such as hydroxyzine, promethazine, cyproheptadine or diphenhydramine, have profound sedating effects that are therapeutically used in sleeping disorders. However, these drugs have long half-lives, and even if taken at bedtime, they may exert their effects at daytime as well, often producing drowsiness. The effect is mediated by blockade of central H1 receptors. Drowsiness alone may affect cognition. In addition, histamine as a neurotransmitter is not only important for keeping us awake, but also plays a central role in cognition, especially learning [63]. Besides that, several first-generation antihistamines have strong anticholinergic properties. The combination of antihistaminic and anticholinergic effects resembles a high risk of cognitive impairment, particularly reduced learning and memory [170, 171]. These drugs should be avoided in the elderly [64].

Acute and chronic effects: Sedation and consecutive negative cognitive effects such as reduced attention may manifest after one dose. Chronic treatment may lead to direct and long-lasting negative effects on learning and memory.

Patient groups at high risk: Older adults, especially those with cognitive impairment and/or treated with other drugs with a potential to induce DICI.

3.9 Drugs for Urinary Incontinence

Traditionally, drugs for urinary incontinence act by blocking muscarinergic M3 receptors on the urine bladder, thus reducing smooth muscle tone. Tolterodine, oxybutynin, and solifenacin are common representatives of this drug class. They pass through the blood–brain barrier and bind to neuronal M1 and M3 receptors with similar affinity as to peripheral M3 receptors [172]. As these receptors are predominantly found in the cortex and the hippocampus, their blocking impairs cognitive functions, particularly memory functions (learning and retrieval), and may lead to dementia-like conditions.

These drugs are classified as drugs with a high anticholinergic burden which means their use poses a high risk of cognitive impairment, delirium, and the development of dementia including Alzheimer’s [171, 173,174,175,176,177]. The risk of dementia increases with greater exposure, possibly even 15–20 years before a diagnosis. However, some studies did not find negative cognitive effects. These studies tended to have shorter follow-up periods or were cross-sectional studies [176].

These drugs should be avoided in the elderly because of their recognised potential to induce cognitive impairment including delirium and dementia [64]. Despite such recommendations from the American Geriatrics Society and others, nearly one-third of dementia patients have urinary incontinence and over one-fourth of them use antimuscarinic drugs [178]. Because of these drugs' potential to impair cognition (and other bothersome anticholinergic adverse effects such as dry mouth etc.), a different class of drugs for urinary incontinence has been developed—β-3-receptor agonists like mirabegron. According to current (limited) knowledge, they do not affect cognition negatively [179].

Acute and chronic effects: Acute delirium may manifest as early as 1 week after treatment initiation but may occur at any time during treatment [180]. Non-acute cognitive effects often start to develop gradually after several weeks of treatment but may manifest earlier or later than that.

Patient groups at high risk: Older adults, especially those with cognitive impairment and/or polytherapy. However, even adults younger than 65 years may experience memory problems.

3.10 Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are notoriously overprescribed, and in many countries, they can be purchased without a prescription [181]. It is not uncommon that patients use these drugs for years. Most meta-analyses did not find conclusive evidence for negative cognitive effects of PPIs. However, one recent, large prospective study demonstrated a 33% increased risk of dementia after use of PPIs for 4.4 years or more [182]. This suggests that cognitive impairment by PPIs is a chronic effect and implies a role of cumulative dose. The results of this study are in agreement with naturalistic studies that found a 44–170% risk increase for cognitive impairment including dementia, dependent on population, comorbidity, and treatment duration [183,184,185,186]. Various mechanisms may be responsible for this, the most important one being strong inhibition of cholinacetyltransferase, the enzyme that synthesises acetylcholine. PPIs inhibit this enzyme with high selectivity and high potency, and at concentrations far below their therapeutic plasma and brain concentrations [187]. A second important mechanism may be the reduced absorption of vitamin B12 because of the anacidity of the stomach [188, 189]. Vitamin B12 plays an important role in neuronal health and has been implied in the pathogenesis of Alzheimer’s disease [190]. Yet another possible mechanism is the induction of endothelial dysfunction which may lead to cardiovascular damage in the brain [191]. Further, PPIs inhibit carbonic anhydrase [192, 193]. Antiseizure medications that inhibit carbonic anhydrase are well known for their pronounced negative effects on cognition, especially verbal memory (see Sect. 3.1*Antiseizure Medications*), while carbonic anhydrase activators are currently being researched for possible neuroprotective effects [194]. Finally, PPIs can induce acute delirium via disturbed electrolyte homeostasis such as hypomagnesaemia, hyponatraemia, or hypokalaemia. This may occur after only one day of treatment [195,196,197]. It is likely, though, that the anticholinergic effects described herein play a causal role in delirium as well.

Acute and chronic effects: One study found that use of PPIs was associated with a 67% increased risk of developing delirium in geriatric patients [198]. Long-term treatment is associated with an increased risk of developing dementia.

Patient groups at high risk: Older adults, particularly those with pre-existing cognitive impairment and/or anticholinergic comedication.

3.11 Glucocorticoids

Elevated cortisol levels are involved in the pathogenesis of delirium, dementia, and age-related cognitive decline. Cerebral atrophy, sometimes irreversible, has long been known as a consequence of treatment with steroids, particularly high-dose treatment [199, 200]. The hippocampus has a high density of glucocorticoid receptors. While short-term exposure to high levels of glucocorticoids may cause reversible hippocampal impairment, chronic exposure may lead to irreversible neuronal death and permanent hippocampal damage [201,202,203,204]. Accordingly, patients receiving chronic treatment with glucocorticoids have reduced hippocampal volumes and exhibit declarative memory deficits [205]. Negative effects on cognition, particularly memory functions, have also been reported in children [206]. Aside from impaired memory functions, executive functions and attention may also be negatively affected [22].

Varney et al. coined the term *steroid dementia* in their 1984 report on six patients (25–65 years old) that experienced dementia without psychotic symptoms while being treated with glucocorticoids [207]. Since then, glucocorticoid-induced cognitive impairment, often mimicking Alzheimer’s, has repeatedly been reported in the literature. Reversal of these symptoms may take from a few weeks to almost a year after stopping treatment [19, 22, 208,209,210].

Acute delirium is common with glucocorticoid treatment. A meta-analysis of 49 studies found that 16% of patients develop delirium [211].

Despite these well documented effects, a recent meta-analysis of 43 RCTs with glucocorticoids found that only one of them looked at possible treatment-emergent cognitive impairment, in line with the recent finding that cognitive safety is largely ignored in RCTs. By contrast, more than half of 22 studies designed to examine adverse cognitive effects of glucocorticoids reported impaired cognition, predominantly memory-related functions (indicating hippocampal damage) [39, 210].

Patient groups at high risk: Older adults, but individuals below 65 years of age may also be affected.

3.12 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) may produce cognitive adverse reactions after a single dose [212, 213]. Interestingly, NSAIDs have been extensively studied as potential protective agents against cognitive decline. For various reasons, the results of these studies have been mixed [214].

Only few studies examined if NSAIDs may induce DICI, and they focused on manifest dementia only. One large study enrolled 2736 dementia-free participants with extensive pharmacy data even from before enrolment and then followed them every other year for up to 12 years. Compared with nonusers and light users, heavy NSAID users had an increased occurrence of dementia (1.7-fold increased) and Alzheimer’s disease (1.6-fold increased) [214]. Heavy use was defined as at least 500 prescribed daily doses within 2 years, equivalent to about five doses a week. Other studies produced negative results. However, they had considerable methodological weaknesses such as short follow-up time or up to 45% of included patients younger than 65 years [215, 216]. In addition, pain itself is associated with impaired cognition [217]. Hence, it can be difficult to identify milder forms of DICI in pain patients, especially with screening tools like the mini mental state examination (MMSE) or the Montreal cognitive assessment (MoCA).

It is not fully understood how NSAIDs may impair cognition. It is possible that NSAIDs have pharmacological effects that have not yet been discovered or that have not been fully elucidated. For example, only recently has it been found that NSAIDs may inhibit the breakdown, and thus prolong the effect, of endocannabinoids [218, 219]. Also, there could be distinct mechanisms for acute and chronic cognitive effects.

Considering the biological effects that we do know most about (inhibition of cyclooxygenase [COX]-1 and -2), the most probable explanation for NSAID-induced cognitive impairment would be that NSAIDs reduce the blood flow to, and within, the brain. This would resemble a parallel to their negative effect on renal blood flow and their potential to induce thrombotic cardiovascular events, that is, constriction of arterioles and enhanced aggregation of thrombocytes [220,221,222]. These mechanisms may cause DICI through acute or chronic neuronal undersupply of nutrients and oxygen as well as unnoticed multiple small strokes.

Acute and chronic effects: Acute treatment may lead to impaired cognition and neurological symptoms. Opticus neuritis with visual field defects after short-term use as well as tunnel vision followed by an altered state of consciousness after a single dose of ibuprofen have been reported [212, 223]. Acute states of pseudo-dementia have been observed after one week of treatment [213]. While several cases have been reported, delirium seems to be a rare complication [224]. Long-term treatment is associated with a 70% increased risk of developing dementia including Alzheimer’s.

Patient groups at high risk: Elderly patients.

3.13 Statins

Cholesterol is an integral part of cell membranes and, as such, important for nerve cell communication [225, 226]. Cholesterol metabolism in neurones and glia cells also plays an important role in memory function. Importantly, cholesterol constitutes around 40% of myelin [227]. Cholesterol is poorly water-soluble and transported in the blood stream as cholesterol-containing lipoproteins (i.e., LDL- and HDL-cholesterol). These do not pass the blood–brain barrier easily. Hence, neurones and glia cells produce their own cholesterol. As brains get older, cholesterol production and myelin formation decrease, both factors contributing to memory deterioration. In Alzheimer's disease, there is a reduction in cholesterol production and its turnover in the brain [225].

Statins pass the blood–brain barrier. Once in the brain, statins reduce cholesterol synthesis the same way they do in the liver [226]. Like with all drugs, the ability of statins to pass over the blood–brain barrier correlates with their lipophilicity. The most lipophilic statin is cerivastatin, followed by simvastatin. The least lipophilic statins are pravastatin and rosuvastatin [226, 228].

By the same mechanism that reduces cholesterol synthesis, statins also reduce the synthesis of coenzyme Q10 (ubiquinone). Coenzyme Q10 has several biological functions, one of which is acting as an intracellular antioxidant. A deficit of coenzyme Q10 may thus contribute to increased neuroinflammation [229, 230].

The effect of statins on cognition is a matter of debate because clinical studies, systematic reviews, and meta-analyses produced conflicting results [231]. It is, however, established that impaired lipid metabolism can affect brain myelination [121]. Moreover, one should distinguish between acute and long-term effects of statins on cognition as they possibly (a) are caused by different mechanisms and (b) may apply to patients with different clinical characteristics [232]. Also, it is possible that statins affect cognitive function by acting on other targets than the cholesterol synthesising enzyme (HMG-CoA reductase), or by (as yet unidentified) indirect mechanisms.

Acute and chronic statin-induced memory loss/amnesia has been documented by numerous case reports, some of them with a so-called challenge-dechallenge-rechallenge design [233,234,235,236]. In some patients, a diagnosis of dementia or Alzheimer’s disease was reversed after stopping the statin [237]. In 2012, the American Food and Drug Administration obliged manufacturers of statins to include reversible cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) in the prescribing information for statins [238]. The hippocampus plays a crucial role in memory functions. Mice receiving chronic simvastatin treatment showed a deficiency in recognition and spatial memory. Imaging studies in these animals revealed a significant decrease of cholesterol in the hippocampus [239].

Regarding long-term effects, several studies found that statins induce cognitive decline [237, 240, 241]. However, many reviews, meta-analyses and position papers did not find detrimental effects and conclude that the beneficial vascular effects of statins outweigh potential cognitive risks [41, 232, 242,243,244,245,246]. Methodological issues, including the documented neglect and underreporting of DICI in RCTs, may explain these divergent results [39]. Moreover, statins may exert a positive effect on cognition by preventing the development of vascular dementia [232]. However, while statins may have a modest effect in slowing the progression of cognitive decline in patients with AD, randomised controlled trials failed to support the beneficial effect of statins in lowering the risk of dementia [225].

Acute and chronic cognitive effects: Statins seem to mainly affect memory functions. Reversible acute amnesia after days to weeks of treatment has frequently been reported. Chronic treatment (months to years) may lead to dementia-like conditions.

Patient groups at high risk: Elderly patients, especially those with existing MCI or dementia (high risk of non-detection of DICI); patients with other cognition-impairing drugs, especially those that affect memory (mainly drugs with anticholinergic effects).

3.14 Antihypertensives and Drugs with Hypotensive Effects

Adequate treatment of hypertension may have a protective effect against dementia but not necessarily against milder forms of cognitive decline [247, 248]. However, hypotension is a common complication of treatment with antihypertensives including β-blockers and diuretics. It is also seen with vasodilating nitrates, tricyclic antidepressants, antipsychotics, dopaminergic antiparkinsonian drugs, benzodiazepines, opioids, and SGLT-2 inhibitors [249,250,251,252,253]. Antihistamines (e.g., diphenhydramine, cetirizine) and herbal supplements (e.g., hawthorn) have only weak to modest hypotensive effects but these may add to hypotensive effects of other drugs [254,255,256,257,258]. Hypotension, often clinically presenting as orthostatic hypotension, is common in hypertensive adults and in the elderly, with prevalences ranging from 3.3 to 58% [259,260,261]. In institutionalised elderly individuals, the prevalence is up to 70% [250].

Individuals with orthostatic hypotension, regardless of age, exhibit deficits in verbal memory and sustained attention. These deficits are predictors of a cognitive decline that surpasses what is typically expected from normal aging [262]. Clinical studies, systematic reviews, and meta-analyses have demonstrated that orthostatic hypotension is associated not only with dizziness but also with falls, ischemic strokes, cognitive impairment, dementia, and increased mortality [249, 260, 263]. Cognitive deficits may manifest in various domains; mainly executive and memory functions are affected.

Acute and chronic effects: It should be noted that acute cognitive effects of orthostatic hypotension may be masked if patients are in the supine position but can become acutely evident when they change to the upright position. This has been reported even in normotensive patients without white matter changes [262]. Chronic hypotension may cause cognitive impairment including dementia, mediated by white and grey matter damage through cerebral hypoperfusion and ischaemia [254,255,256,257,258].

Patient groups at high risk: Patients in all age groups with normotensive or hypotensive orthostatic hypotension.

3.15 Chemotherapeutic Agents

Patients treated for CNS and non-CNS cancers often report cognitive symptoms such as impaired attention, memory, executive functions, and processing speed. This is commonly called cancer-related cognitive impairment (CRCI). CRCI is very frequent in both adults and children; for example, 15–25% of breast cancer patients show objective cognitive impairment after chemotherapy, as well as up to 32% of children with acute lymphoblastic leukaemia [264,265,266].

Patients commonly refer to CRCI as ‘chemofog’ or ‘chemobrain’. However, some patients may already have cognitive problems before treatment, especially those with CNS tumours. Receiving a cancer diagnosis and related treatment can be emotionally distressing. An association between depression or anxiety and cognitive complaints by cancer patients has been found in many studies [6, 267]. On the other hand, a solid body of evidence shows that cancer treatment can induce acute and long-term cognitive impairment [6, 264, 266]. Patients typically return to baseline within 6 months to 2 years post-treatment, although nearly one-third may experience persistent cognitive dysfunction [266, 268]. Interestingly, one meta-analysis on long-term cognitive outcome in cancer survivors found CRCI in cross-sectional studies but not longitudinal studies. This was probably caused by methodological issues including a practice effects of repeated neuropsychological testing [269].

A variety of mechanisms for drug-induced CRCI have been suggested [270]. Most importantly, chemotherapy can trigger an inflammatory response in the body, including the brain. High levels of proinflammatory cytokines are associated with cognitive dysfunction [268, 271]. Inflammation-related oxidative stress can damage neurones and glia cells [6, 272]. Furthermore, the blood–brain barrier becomes leaky, allowing harmful agents to enter the brain [273]. Second, most cancer drugs that enter the brain decrease hippocampal neurogenesis. This impairs cognitive function, especially learning and memory [274]. Third, cancer treatment with cytokines like interferon-α can produce cognitive impairment including memory disturbances [275]. Fourth, hormone therapies for breast or prostate cancer reduce sex hormone production or act antagonistically on sex hormone receptors. However, these receptors are also found in the brain’s cortex and in the hippocampus where they play a role in cognitive function. Thus, it is possible that such therapies induce or contribute to CRCI [6, 268].

Acute and chronic effects: Delirium is a common complication in cancer patients. CRCI is even more common.

Patient groups at high risk: Patients with CNS tumours; those with advanced cancer; those with psychoactive medications including opioids, benzodiazepines, corticosteroids; elderly patients, especially those with dementia.

4 Discussion and Conclusions

The aim of this review was not to weigh the pros against the cons, to impose dos and don’ts, or to quantify any risks, but rather to demonstrate that cognitive impairment may be induced by many different drug classes, and to raise awareness. While the evidence level is highly variable, many drug classes have a demonstrated potential to induce, or are associated with an increased risk of various acute and chronic types of cognitive impairment. Compared with research on delirium or manifest dementia in the elderly, there is little research on milder forms of DICI, especially in younger populations. It cannot be stressed enough that DICI is not synonymous with dementia or delirium, and that it occurs not only in the elderly but also in younger adults and in children, for example reduced verbal memory induced by antiseizure medications. While a false diagnosis of dementia stands out as the worst case, even subtle forms of DICI can have deleterious, life-long consequences if they are not recognised correctly. Missed degrees and careers due to reduced performance in school or university, losing work, broken relationships, losing the right to care for one's child or to manage one's own private economy are examples of such consequences.

Moreover, much of the published research on DICI consists either of observational studies or of meta-analyses of clinical trials. The inherent limitations of observational studies are well known. It is, thus, very unfortunate that there is a considerable lack of high-quality cognitive data on DICI from prospective, controlled clinical trials: only 6.5% of clinical drug trials actively assess the cognitive safety of the trial drug. Of those few trials, most use inadequate methods and have a significant publication bias leading to underreporting of DICI [39]. This makes systematic reviews and meta-analyses prone to produce false-negative results.

It is unlikely that drug manufacturers are not aware of the problem posed by inadequate cognitive assessment methods. This is illustrated by the fact that drug trials intended to demonstrate beneficial cognitive effects of the trial drug consistently use extended neuropsychological test batteries instead of simple screening instruments like the MMSE or MoCA (the authors; data obtained from www.clinicaltrials.gov).

Given the above and given the epidemiology of cognitive impairment including its predicted future development, more research on DICI is urgently needed. Primarily, regulatory authorities should require an active assessment of cognitive function in all drug trials, performed with adequate methods. Like monitoring of cardiovascular function and lab values, active monitoring of cognitive function should be part of all drug trials. Relying on spontaneous reporting or the sole use of questionnaires or screening tools such as the MMSE or MoCA to assess the cognitive safety of drugs is inadequate. We recommend specific assessment of each cognitive domain. Ideally, an experienced neuropsychologist should select the tests. This should be mandatory for drugs known to, intended to, or suspected to affect the CNS, including drugs with a primary target outside the CNS. For all other drugs, domain-specific cognitive screening tools should be used. They should be selected according to the study population as well as the condition and drug studied. Examples for appropriate tools include EpiTrack®, the Rowland Universal Dementia Assessment Scale (RUDAS), or the Mini-Cog®.

Apart from active assessment of cognitive safety in drug trials, raised awareness of DICI among health care professionals is a necessity. DICI should become a regular differential diagnosis in all kinds of cognitive impairment in patients receiving drug treatment.

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