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SYSTEMATIC REVIEW

Drug-Induced Intracranial Hypertension: A Systematic Review and Critical Assessment of Drug-Induced Causes

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Abstract

Background Idiopathic intracranial hypertension (IIH) is a condition with increased intracranial pressure of unknown etiology. Its presenting symptoms include persistent headache, pulsatile tinnitus, and visual obscuration. It tends to occur in obese women of childbearing age, and its greatest risk is irreversible loss of vision. Some of the commonly used medications in dermatology, especially those for acne vulgaris, have been associated with IIH. However, the creation of specific risk categories for drugs as a guide for clinicians has never been performed.

Objective The aim of this study was to critically assess all published cases of IIH and identify high-risk drugs associated with drug-induced intracranial hypertension (DIIH), to assist dermatologists and other physicians with patient education and monitoring of symptoms of secondary intracranial hypertension.

Methods MEDLINE, EMBASE, and Cochrane Review Databases were searched for all cases of IIH thought to be drug-related between January 1900 and June 2019. A total of 5117 articles were identified, and 235 articles were found to be relevant. All cases were assessed to satisfy the modified Dandy criteria for diagnosis of IIH, and the likelihood of each case being a 'definite' adverse drug reaction (ADR) was determined using the Koh algorithm for ADR. An association category (from weakly associated [Category I] to strongly associated [Category V]) was assigned based on the number of cases meeting these two criteria.

Results There were 259 verifiable cases of DIIH. Vitamin A derivatives, tetracycline-class antibiotics, recombinant growth hormone, and lithium were found to be most strongly associated with DIIH (Categories IV and V). Corticosteroids were moderately associated with DIIH (Category III). Drugs that were weakly associated with DIIH (Categories I and II) include cyclosporine, progestin-only contraceptives, combined oral contraceptives, second- and third-generation fluoroquinolones, sulfenazone, gonadotropin-releasing hormones and luteinizing hormone-releasing hormone agonist, nalidixic acid, amiodarone, stanozolol, danazol, divalproic acid, sulfasalazine, ketoconazole, and ustekinumab.

Conclusion We suggest using the term 'drug-induced intracranial hypertension' (DIIH) and propose a set of diagnostic criteria for DIIH. Our review attempts to identify DIIH-associated drugs based on a strict diagnostic and drug-causality algorithm, then stratify them into appropriate risks categories. This may ultimately assist physicians in counselling patients about the risk of DIIH when prescribing medications and recognizing this uncommon yet sight-threatening condition.

Key Points

Drug-induced intracranial hypertension (DIIH) should be used to describe intracranial hypertension that is precipitated by medications.

Drugs that were most strongly associated with DIIH include vitamin A derivatives, tetracycline-class antibiotics, recombinant growth hormone and lithium.

Patients who are initiated on high-risk medications should be educated on the signs and symptoms of intracranial hypertension.

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1 Introduction

1.1 How Does Idiopathic Intracranial Hypertension (IIH) Present?

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri syndrome, presents with symptoms of headache, pulse synchronous tinnitus, and transient visual obscurations. The headaches reported are often atypical: predominantly frontal in location, worse in supine, and more prominent when first awakening. These symptoms result from an elevation in intracranial pressure (ICP) of unknown cause. Neuroimaging and cerebral spinal fluid (CSF) analysis are normal except for elevated lumbar puncture opening pressure.

IIH is most commonly reported in females of childbearing age and with high body mass index [1]. Mimickers of IIH include venous sinus thrombosis, autoimmune diseases (e.g. systemic lupus erythematous, Behçet disease), and central nervous system (CNS) infections.

A thorough examination of the optic disc, visual function, and ocular alignment is critical for the diagnosis of IIH. Occasionally, there is mild paresis of the abducens nerve, resulting in an abduction deficit of the ipsilateral eye. Unrecognized IIH can lead to permanent vision loss.

The Dandy criteria for the diagnosis of IIH was first proposed in 1937 by Dandy. In 2013, Friedman et al. proposed revisions to improve the diagnostic accuracy of IIH [1]. The modified Dandy criteria raised the required lumbar puncture opening pressure to 250 mmH_2O, removed the necessity of papilledema, and incorporated neuroimaging features (Appendix 1, see electronic supplementary material [ESM]).

1.2 What Medications are Thought to Induce IIH?

Medications that are commonly used for the treatment of acne and other inflammatory dermatoses, such as tetracycline-class antibiotics, oral contraceptives, systemic corticosteroids, and vitamin A derivatives are implicated to cause IIH [2]. A critical evaluation examining the veracity of reputed drug-induced intracranial hypertension (DIIH) case reports is needed to assist physicians to safely manage and advise patients with IIH. Patients presenting with IIH who are being treated with medications that are determined to be in the high-risk category should be considered to have DIIH.

In this review, we critically evaluated all reported cases of DIIH and created a case-based census that attempts to establish causality and assess the risk for each of the reported medications. Our review will assist dermatologists and other physicians with patient counselling and making the decision to discontinue a medication when appropriate.

2 Methods

2.1 Data Sources and Searches

We conducted a literature search to determine the strength of association between different medications and IIH. We consulted with a librarian and searched MEDLINE, EMBASE, and Cochrane Review Databases for cohort studies, case series, and case reports. 'Idiopathic intracranial hypertension', 'pseudotumor cerebri', 'benign intracranial hypertension', and focused search terms for study type were used to capture different types of observational studies between January 1900 and June 2019.

2.2 Study Selection

The search results were narrowed first by title, followed by abstract, and then full texts were reviewed. All references from review articles were evaluated for eligible studies. Studies were considered for inclusion if they were observational studies involving patients with IIH and a drug was implicated as the cause.

2.3 Data Extraction and Indexing of Cases

A total of 5117 primary articles were identified initially, of which only 235 articles were found to be relevant (Fig. 1). Each article was analyzed for eligibility based on fulfilling the following two requirements: (i) modified Dandy criteria for the diagnosis of IIH (Appendix 1, see ESM), and (ii) the Koh algorithm probability score for 'definite' adverse drug reaction (ADR) (Appendix 2, see ESM) [1, 3].

The Koh algorithm for ADR is a causality assessment tool that can be used to establish causality between a drug and an adverse event [3]. This algorithm has a sensitivity and specificity of 83.8% and 71.0%, respectively, for detecting causality [3]. A probability score of ≥ 0.75 (out of 1.0) on the Koh algorithm was used to define 'definite' ADR. This corresponds to seven rules, each rule with its own set of criteria, from the Koh algorithm that can be used to define 'definite' ADR (Appendix 2, see ESM). Although not perfect, the Koh algorithm is superior to other algorithms, such as the Naranjo algorithm or the Adverse Drug Reactions Advisory Committee (ADRAC) algorithm, in assessing causality between a drug and an adverse event [3].

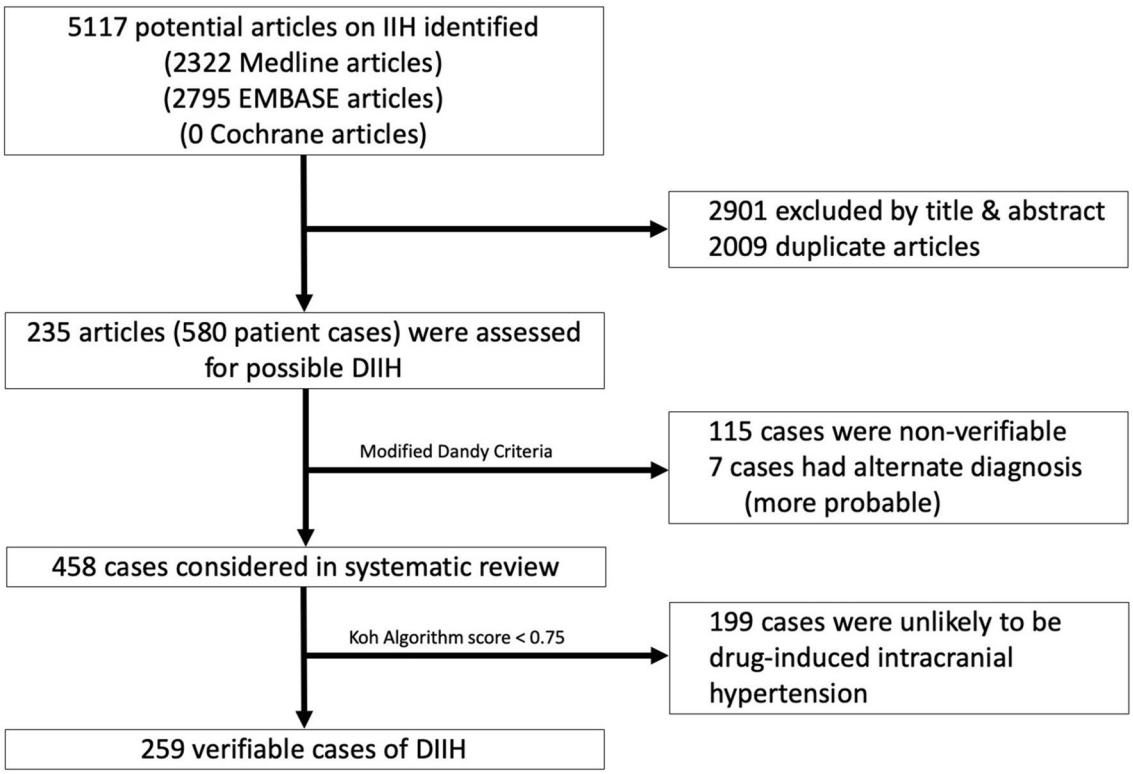

Fig. 1 PRISMA flow diagram. This flow diagram depicts how articles identified from MEDLINE, EMBASE and Cochrane Review Database were screened, included or excluded (including reasons for exclusion) from this systematic review

All cases were discussed amongst reviewers where needed to resolve any disagreements. Where there was insufficient information to assess a case for its inclusion, we attempted to contact the corresponding authors for further information. English translation of articles was sought when necessary. We adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines where applicable [4].

2.4 Data Synthesis and Analysis

All medications that were possible causes of IIH were reviewed for inclusion. The absolute number of cases found in the literature that met diagnostic criteria of IIH and the Koh algorithm probability score of 'definite' ADR were reported (Fig. 1). Drug-induced cases that did not meet these requirements were not included in the total case count to prevent bias. Defining attributable risk was not possible, as data for the number of prescriptions for each medication in each year of inclusion was not available. Instead, case-census categories were created to reflect the number of cases of IIH for a specific medication. Since this analysis does not include prescribing rate, it only approximates the true association of each medication. This serves as a framework to assist clinicians in stratifying these medications into various risk categories.

2.5 Data Availability Statement

All results related to this study are presented in this article. The studies included in this systematic review are listed in a table (Supplementary Table 1, see ESM).

3 Results

The PRISMA flow diagram in Fig. 1 illustrates how articles identified from MEDLINE, EMBASE and Cochrane Review Databases were screened, included, excluded, and reasons for exclusion. There were 259 verifiable cases of drug-induced intracranial hypertension that met the modified Dandy criteria and Koh algorithm for 'definite' adverse reaction. A summary of our findings is listed in Table 1. Drug classes are listed according to number of verifiable cases in their respective association categories: Category V (≥ 20 cases), Category IV (15–19 cases), Category III (10–14 cases), Category II (5–9 cases) and Category I (1–4 cases). These five categories were derived

based on the number of cases of DIIH that met two inclusion criteria.

Category V medications included Vitamin A and its derivatives, tetracycline-class antibiotics, and recombinant growth hormone. A total of 84 verified cases of DIIH from vitamin A and its derivatives were found: 25 cases from excess vitamin A supplementation, 44 cases from systemic tretinoin use, and 15 cases from systemic isotretinoin use. A total of 71 cases of DIIH from tetracycline-class antibiotics were found: 32 were from minocycline, 24 were from tetracycline, and 15 were from doxycycline. Twenty-four cases of DIIH resulting from recombinant growth hormone use were found.

Category IV medication includes lithium. Seventeen cases of lithium were found to be associated with DIIH. Category III medication includes corticosteroids. A total of 14 cases of corticosteroids were implicated in DIIH.

Category II medications include sulfenazone, first-generation fluoroquinolone, cyclosporine, gonadotropin-releasing hormone (GnRH)/luteinizing hormone-releasing hormone (LHRH) agonists, amiodarone, and progestin-only contraceptives.

Category I medications include second- and third-generation fluoroquinolones, combined oral contraceptive pills, stanozolol, danazol, divalproic acid, sulfasalazine, ketoconazole, and ustekinumab.

Table 1 Summary of cases of IIH related to individual medications

Category (no. of verified cases)	Medication class		Patients	Associations/comments
V (≥ 20 cases)	Vitamin A and derivatives	Vitamin A supplementation	84	Excessive vitamin A supplementation, treatment for acne
		Isotretinoin		
		Tretinoin		
	Tetracycline-class antibiotics	Minocycline	71	Treatment for acne, malaria prophylaxis
		Tetracycline		
		Doxycycline		
	Recombinant growth hormone		24	In children or among athletes (doping)
IV (15–19 cases)	Lithium		17	
III (10–14 cases)	Corticosteroids		14	In children DIIH occurs after withdrawal from chronic use
II (5–9 cases)	Sulfenazone		9	
	First-generation fluoroquinolone	Nalidixic acid	7	
	Cyclosporine		7	
	GnRH/LHRH agonists	Leuprorelin	6	
		Triptorelin		
	Amiodarone		5	
	Progestin-only contraceptives	Norplant®	4[a]	Subcutaneous implantable device
		Nexplanon®		
I (1–4 cases)	Second- and third-generation fluoroquinolones	Ciprofloxacin	4	Cases in this category may be coincidental
		Levofloxacin		
		Ofloxacin		
	Combined oral contraceptives		3	
	Stanozolol		1	
	Danazol		1	
	Divalproic acid		1	
	Sulfasalazine		1	
	Ketoconazole		1	
	Ustekinumab		1	

DIIH drug-induced intracranial hypertension, *GnRH* gonadotropin-releasing hormone, *IIH* idiopathic intracranial hypertension, *LHRH* luteinizing hormone-releasing hormone

[a]Many reports exist, including case–control studies, that cannot be verified for accuracy. To account for this, progestin-only contraceptives has been promoted to a higher category than its raw case count

4 Discussion

4.1 Category V (≥ 20 Verifiable Cases)

4.1.1 Vitamin A and Derivatives

Vitamin A derivatives are commonly used in dermatology and for treatment of leukemia and lymphoma in oncology. From the 84 verified cases of DIIH associated with vitamin A and its derivatives, the onset of symptoms occurred within days of initiating treatment. Vitamin A and its derivatives alter sensitivity to the 11β-hydroxysteroid pathway, resulting in increased CSF production and reduced reabsorption by the arachnoid body [5, 6]. Patients on vitamin A therapy should be encouraged to avoid further vitamin A supplementation because of additive effects.

Vitamin A is metabolized into different metabolites, including all-trans retinoic acid, 9-cis retinoic acid, and 4-oxoretinoic acid metabolites. These metabolites are the active ingredients used in commercial retinoids.

4.1.1.1 Vitamin A Supplementation Supplementation of vitamin A in excess of 25,000 IU or consumption of liver from game animals can result in hypervitaminosis A. Hypervitaminosis A syndrome is characterized by xerosis, alopecia, migratory arthralgias, amenorrhea, and hepatosplenomegaly. Reports indicate that DIIH occurred in 50% of cases with hypervitaminosis A [7]. Of the 25 cases of DIIH reported due to excess vitamin A supplementation, one was related to concurrent vitamin A supplementation with isotretinoin for acne [8]. Hypervitaminosis A appeared to occur more frequently in children and infants. The propensity for hypervitaminosis A in younger children may be secondary to reporting bias, lower body fat content that increases bioavailability, or lower excretion of active metabolites compared with adults.

4.1.1.2 Isotretinoin Isotretinoin is most commonly used to treat acne vulgaris, although it can also be used to treat other disorders such as psoriasis. Its mechanism of action is complex and remains under investigation. All 15 cases of DIIH associated with isotretinoin occurred in patients aged 14–38 years old and in the context of treating acne. The latency to onset of DIIH from isotretinoin was 4–8 weeks [9]. Among the 15 cases of DIIH with a definite link to isotretinoin, six cases were re-challenged with isotretinoin and their symptoms of increased ICP recurred. Two of the fifteen cases were associated with concomitant use of tetracycline-class antibiotics [10].

A physician-reporting database attributed a further 173 cases of DIIH to isotretinoin, with 153 cases having documented resolution after withdrawal of isotretinoin only. The remaining 20 cases had little information available, hence the diagnosis of DIIH could not be verified [11].

The DIIH association between isotretinoin and tetracycline-class antibiotics resulted in the recommendation of a 7-day washout between tetracyclines and isotretinoin at minimum [12]. This was based on a theoretical calculation of seven half-lives to achieve 99% drug clearance after steady state. This recommendation has not been verified in clinical practice.

4.1.1.3 Tretinoin (All-trans Retinoic Acid) Tretinoin is a principal metabolite of vitamin A and is commonly used in topical formulations for the treatment of acne. Tretinoin is also used in systemic chemotherapy regimens for the treatment of acute promyelocytic leukemia. There were 44 cases where tretinoin was found to be associated with DIIH. These cases occurred in patients of all ages, and only one patient was found to be obese. Combining data from multiple acute leukemia studies, it appears that approximately 9% of patients developed symptoms of increased ICP during treatment with tretinoin.

4.1.1.4 Other Vitamin A Derivatives (Acitretin, Etretinate, Alitretinoin, and Bexarotene) Symptoms of increased ICP were rarely reported in patients using acitretin or etretinate. None of the five case reports met the two inclusion requirements. Acitretin is less lipophilic and has less cardiovascular risk than its prodrug etretinate. These two medications have a wide range of indications but are most often prescribed for the treatment of psoriasis. Etretinate was withdrawn from the North America market due to its significant teratogenicity and long half-life. Alitretinoin and bexarotene are two other retinoids that have no reports of increased ICP that met the criteria for inclusion as DIIH. Given the fewer reports of DIIH in association with acitretin, etretinate, alitretinoin, and bexarotene based on the current literature, it is possible these medications do not alter choroid plexus and arachnoid granulation physiology.

4.1.2 Tetracycline-Class Antibiotics

The tetracycline-class of antibiotics has indications for infectious and non-infectious disorders. Some indications for tetracycline-class antibiotics include chemoprophylaxis for malaria, and treatment of bullous pemphigoid, acne, leprosy, Lyme borreliosis, and methicillin-resistant staphylococcus aureus.

Minocycline, tetracycline, and doxycycline have all been associated with DIIH, with both immediate and delayed presentations. A short latency to onset of DIIH has been described in tetracycline-class antibiotics from 2 weeks to 2 months of initiation [2, 13]. When tetracycline-class

antibiotics use exceeded 6 months' duration, there has been delayed presentation of DIIH of up to 1 year. There are no reports of third-generation tetracycline-class antibiotics (tigecycline) causing DIIH. This may be due to its distinct chemical structure, or due to a lack of reporting as it has only been available since 2005.

It is important to note that combining tetracycline-class antibiotics with retinoids or lithium in high-risk individuals has compounded the risk for DIIH in case reports [14, 15]. It is possible that given the rare reports this could be of negligible concern. Counseling patients on the symptoms of elevated ICP can be a reasonable step in high-risk patients. The suggested 'washout period' of 7 days when switching between tetracycline-class antibiotics and isotretinoin was based on a theoretical pharmacologic calculation of seven half-lives to achieve 99% drug clearance after steady state, rather than clinical evidence from practice [16].

4.1.2.1 Minocycline Minocycline's association with DIIH is the strongest in the tetracycline-class antibiotics. Nearly all of the 32 reported cases of minocycline-related DIIH occurred during acne treatment and women of childbearing age were overrepresented. It is important to note that there are reports of patients who had discontinued minocycline due to DIIH and then started on isotretinoin several years later without recurrence of DIIH [14, 17].

4.1.2.2 Tetracycline There were 24 verifiable cases of DIIH associated with tetracycline use and involved both adult and adolescent patients. However, those who developed DIIH while receiving tetracycline for acne cases were adolescents. One patient who was on tetracycline for 7 months for the treatment of acne presented with delayed DIIH 1 month after discontinuing this medication [18].

4.1.2.3 Doxycycline Among the tetracycline-class antibiotics, doxycycline had the fewest reports of DIIH. All 15 cases reported in the literature met diagnostic criteria. The largest case series included seven patients, four of whom were obese [19]. DIIH occurred in patients receiving doxycycline with longer treatment courses, such as the treatment of acne or malaria prophylaxis. Short courses were not associated aside from one patient treated for Lyme borreliosis.

4.1.3 Recombinant Growth Hormone

DIIH was reported in 24 pediatric patients with renal insufficiency or genetic growth impairment who were receiving recombinant growth hormone. These 24 cases were related to frequent or higher doses of recombinant growth hormone. There were no reported cases in adults.

4.2 Category IV (15–19 Verifiable Cases)

4.2.1 Lithium

The 17 cases of DIIH associated with lithium use occurred in adults and children. Their serum levels of lithium measured were within the therapeutic range. Lithium can compete with sodium for its channels; hence, it is feasible that DIIH could occur though altering CSF production. This mechanism has not been directly studied and remains theoretical.

4.3 Category III (10–14 Verifiable Cases)

4.3.1 Corticosteroids

Corticosteroids are frequently used for their anti-inflammatory or immunosuppressive properties. The reports of DIIH occurred when corticosteroids were withdrawn, especially in children. Twelve reported cases of DIIH occurred in children after withdrawal of systemic corticosteroid for bronchitis or asthma. In addition, two infants developed DIIH after cessation of a long course of topical betamethasone valerate ointment. Both of these infants had compromised skin barrier integrity (one had generalized congenital ichthyosis and the other had undiagnosed candida diaper dermatitis) that may have resulted in increased transepidermal absorption.

Other cases of IIH occurred in patients with inflammatory bowel disease treated with prednisone and budesonide [20, 21]. These cases of IIH, including the only adult case reported with prednisolone, were unlikely to be related to corticosteroids as there were other more probable explanations for their elevated ICP. In addition, budesonide is an unlikely cause of DIIH as it has very low bioavailability due to a hepatic first-pass metabolism of > 90%. Additional pharmacosurveillance for corticosteroids would help to clarify its association category with DIIH.

Overall, DIIH associated with corticosteroid use is seen in pediatric patients who are being withdrawn from corticosteroids. Nonetheless, DIIH is a rare adverse effect relative to the widespread use of corticosteroids.

4.4 Category II (5–9 Verifiable Cases)

4.4.1 Sulfenazone

Sulfenazone, an old sulfa antibiotic, was found to be responsible for DIIH in nine Italian infants and adolescents. These cases were generally transient and without long-term consequences. DIIH is unlikely to be related to the sulfa group, since acetazolamide, which has a similar sulfa group, is a treatment for DIIH.

4.4.2 Nalidixic Acid

Of the 11 cases of fluoroquinolone-induced DIIH found, seven cases were attributed to nalidixic acid, a first-generation fluoroquinolone that is typically used in low-resource countries. Adults and children were affected while undergoing treatment for non-CNS infections. Though fluoroquinolones are a less probable cause of DIIH, it is more of a concern with nalidixic acid. Similar to corticosteroids, further reports will clarify their association.

4.4.3 Cyclosporine

Cyclosporine is approved for the prevention of rejection post-organ transplantation and the treatment of psoriasis. It is also listed as an approved indication for atopic dermatitis in some countries. Its off-label uses are diverse. Of the seven cases of DIIH associated with cyclosporine, three patients had cyclosporine for allogenic bone marrow transplantation, two for renal transplant, one for atopic dermatitis, and one for tubulointerstitial nephritis. Patients who developed DIIH while on cyclosporine were younger and received a mean dose of 3 mg/kg. There was no bias for weight or gender. One obese boy developed DIIH after being on cyclosporine for 6 months.

The pathophysiology of DIIH from cyclosporine is unknown. Cases are still being reported as recently as 2015. An association may be emerging. It is interesting to note that there were no reports of DIIH occurring in renal transplant patients on cyclosporine who were concurrently receiving systemic vitamin A derivatives like acitretin for the chemoprevention of skin cancers.

4.4.4 GnRH/LHRH Agonists

GnRH/LHRH agonist-associated DIIH occurred in three adults (for prostate cancer and menorrhagia) and three children (for precocious puberty) who received leuprorelin or triptorelin. There was no gender, age, or weight bias. None of the cases had any sequelae after the GnRH/LHRH agonist was discontinued. These medications are likely to be low risk for DIIH.

4.4.5 Amiodarone

Five cases of DIIH were reported to be associated with amiodarone, with no new reported cases since 2003. Every case occurred in men receiving amiodarone for ventricular arrhythmias, either as a primary or secondary prophylaxis. These patients did not possess the traditional risk factors (young age or obese females of childbearing age). There was prompt resolution of symptoms after discontinuation of amiodarone, suggesting that amiodarone was possibly implicated. The pathophysiology of amiodarone-associated DIIH remains unclear. Inhibition of potassium efflux should not significantly change CSF production or reabsorption. It is uncertain whether these cases were incidental, but it was difficult to discount them based on their presentation. There have been no reports of IIH with dronedarone, a chemically similar class III antiarrhythmic, which makes a link between amiodarone and IIH questionable.

We also advise caution in interpreting these cases as DIIH, as there is significant overlap in the presentation of increased ICP and amiodarone-induced optic neuropathy. The case from 2003 was particularly concerning for misclassification bias.

4.4.6 Progestin-Only Contraceptives

Progestin-only contraceptives, compared with combined oral contraceptives, may have a stronger association with DIIH. It first emerged with post-market surveillance of an implantable contraceptive (Norplant®) that was globally discontinued in 2008 in favor of newer products that are easier to insert and remove. In total, 42 cases of IIH were found, of which only four cases reported resolution of elevated ICP symptoms after removal of the drug. Possible risk factors such as weight were not taken into account.

A case–control study with levonorgestrel intrauterine devices (Mirena®), without adjusting for covariates, found an odds ratio of 3.4 in 21 patients with IIH [22]. Another retrospective case–control study of 59 patients with IIH who completed a birth control history had an OR of 2.87 when adjusted for weight by sensitivity analysis [23, 24]. However, sensitivity analysis cannot account for unknown relationships between variables, and much of the information was based on databases and diagnostic coding [25]. None of these studies satisfied the Koh algorithm based on the information that was available, and hence were excluded. Overall, it is difficult to assign progestin-only contraceptive to one of the risk categories. Despite having only four verifiable cases, a Class II association was given due to the numerous reports. Further reporting with strict adherence to the diagnostic criteria of IIH is needed for progestin-only contraceptive.

4.5 Category I (1–4 Verifiable Cases)

4.5.1 Second- and Third-Generation Fluoroquinolones

Of the eleven cases of fluoroquinolone-induced IIH found, only four cases involved second- and third-generation fluoroquinolones: ciprofloxacin, levofloxacin, and two with ofloxacin. Just like others in Class I, given the rare reports, it is may represent a sporadic association. The potential risk

of DIIH with fluoroquinolones may rest with nalidixic acid alone.

4.5.2 Combined Oral Contraceptive (OCP)

Nearly all cases of increased ICP associated with OCP use have been reported in obese women of childbearing age. This was especially true in the 1970s and 1980s. OCPs, especially those with combined hormones, have been traditionally associated with elevated ICP. Only two verified cases of DIIH were linked temporally with the initiation of OCP and resolution with its discontinuation. A single case of IIH following the use of emergency oral contraceptive (Tetragynon®) was also reported. Based on larger case–control studies for patients with risk factors, OCP use was no more prevalent in those with DIIH than in healthy age-matched controls [26, 27]. Given that case–control studies also show no increased incidence of IIH in pregnancy, where estrogen and progesterone levels are high, the association of OCPs with DIIH is weak [28]. It is possible that the above cases represent a coincidental association. Unrecognized venous sinus thrombosis is also an important consideration in these patients [29].

4.5.3 Other Medications

Trimethoprim-sulfamethoxazole has been reported in four cases meeting the diagnostic criteria for IIH, but these failed to meet a sufficient Koh algorithm score for causality of an adverse drug event. Sulfa antibiotics have an unlikely association with IIH.

Anabolic steroid derivatives (stanozolol, danazol), divalproic acid, sulfasalazine, ketoconazole, and ustekinumab all have a single case report each and are probably spurious associations. Given the extensive use of divalproic acid, sulfasalazine, and ketoconazole, it is surprising that more cases have not been reported. These cases could not be excluded based on their clinical presentations. Ketoconazole was used as a cortisol-lowering therapy in an adult patient with persistent Cushing's disease, suggesting that a decrease in serum cortisol could contribute to the development of DIIH.

Reports of risperidone, phenytoin, nitrofurantoin, and levothyroxine were all excluded as they were likely coincidental exposures. There is no clear link to the syndrome on their own. The patients on risperidone had significant weight gain prior to the onset of IIH, rather than the drug directly causing the disease [30]. Withdrawal of these medications did not correlate with the resolution of symptoms.

A case of DIIH occurred 6 months after a female patient was initiated on ustekinumab (after her 4th dose) for the treatment of moderate-to-severe psoriasis and resolved within five half-lives after the medication was discontinued. This probably represents a spurious association although it cannot be excluded based on the presentation. Biologics are a relatively novel class of medications and additional pharmacosurveillance in the future would be required.

A case of IIH occurred after peripherally injected desmopressin [31]. However, the patient had multiple risk factors for IIH. Desmopressin, when injected peripherally, does not enter the CSF or CNS in significant quantities. This ADR was more likely incidental than drug-related and hence was excluded.

4.6 Proposed Diagnostic Criteria for DIIH

The diagnostic criteria for drug-induced intracranial hypertension (DIIH) has not yet been proposed. Adapting from the modified Dandy criteria and using rule #4 for 'definite' ADR from the Koh algorithm for ADR (Appendix 2, see ESM), we propose a set of diagnostic criteria for DIIH (Table 2) [3]. A typical 'definite' ADR according to the Koh algorithm would include the following features: (i) presence of temporal effect between administration of suspected drug and onset of ADR, (ii) ADR has been associated with suspected drug before, (iii) ADR cannot be explained by any existing clinical condition, (iv) improvement of ADR upon discontinuation of suspected drug, and (v) if a re-challenge with suspected drug is performed, the results must not be negative. Since re-challenge of the suspected is not always feasible nor recommended, we propose that when at least four of the five criteria in Table 2 are met, then the diagnosis of DIIH should be considered.

4.7 Suggested Management of DIIH

If patients experience symptoms of increased ICP, they should be strongly advised to seek immediate medical attention from their prescribing physician for an evaluation. If DIIH is suspected by the prescribing physician, an immediate referral to a neurologist and/or an ophthalmologist for co-evaluation and co-management is strongly recommended to mitigate the risk of vision loss [32]. Cerebral computed tomography, magnetic resonance imaging, or other forms of neuroimaging may be required to rule out other causes of increased ICP. A lumbar puncture should also be performed to measure the opening pressure and evaluate CSF composition.

The first step in the management of DIIH should be the prompt discontinuation of the offending medication. However, discontinuation of the offending medication is usually insufficient, and patients often require further treatment [32]. Potential treatments may include CSF suppressants (acetazolamide), low-sodium weight reduction diet, CSF diverting procedures (shunting or stenting) and/or optic nerve

Table 2 Proposed diagnostic criteria for drug-induced intracranial hypertension

A diagnosis of DIIH can be made if the patient meets the diagnostic criteria for IIH (Appendix 1, see ESM) *and* at least four of the following:	
A	Signs or symptoms of increased ICP are not due to any pre-existing clinical condition[a]
B	Signs or symptoms of increased ICP developed within a reasonable time interval of drug administration
C	Upon discontinuation of suspected drug, signs or symptoms of increased ICP improved after five half-lives[b] with subsequent resolution
D	Signs or symptoms of increased ICP recurred on re-challenge of suspected drug
E	The suspected drug has been previously reported to be associated with increased ICP

DIIH drug-induced intracranial hypertension, *ESM* electronic supplementary material, *ICP* intracranial pressure, *IIH* idiopathic intracranial hypertension

[a]Pre-existing clinical condition refers to any clinical condition which could mimic the findings of increased ICP, such as venous sinus thrombosis, autoimmune diseases, or CNS infections

[b]Five half-lives would correspond to an approximate drug clearance of 97%

fenestration [33, 34]. If DIIH occurs with one medication, other drugs associated with DIIH should be used with caution and close surveillance undertaken for a recurrence of DIIH.

5 Limitations

Our review is only as sensitive and specific as the modified Dandy criteria used to establish the diagnosis of IIH, and the Koh algorithm for ADR used to determine the probability of drug causality. The association class assignment by our method accounts for some uncertainty and is open for revision as more information becomes available. It is important to note that this study only evaluated the associations between medications and increased ICP. Association should not be interpreted as equivalent to causation. A majority of DIIH cases are limited to case reports or case series. It is unclear if this represents an under reporting or a weak association.

Future studies to build on current work could establish other elements of causality including the consistency, specificity, and temporality of the association. Additional studies are required to assess whether a biological gradient effect exists, whether there are plausible explanations for each of the associated medications, and whether there exist additive effects of higher risk medications when these are administered concurrently. The latter would be of particular interest to dermatologists, who regularly co-administer drugs associated with DIIH such as oral contraceptives with isotretinoin or cyclosporine. Establishing pharmacovigilance databases for cases of DIIH is necessary to answer these questions.

6 Conclusion

We performed a systematic review of the associated medications and classified each agent according to their likely association with DIIH. We also proposed a set of diagnostic criteria for DIIH, adapted from the modified Dandy criteria for IIH and the Koh algorithm for ADR. Reporting of adverse events from drugs is critical, but skepticism is necessary when risk factors for IIH are present concomitantly.

DIIH is an uncommon but important adverse reaction of some medications. Physicians should also be aware of the strength of association associated with each of the reputed DIIH medications, and exercise caution when prescribing them. Patients who are starting on DIIH-associated medications should be informed about the risk of this unpredictable ADR. In particular, high-risk patients (obese females of childbearing age) should be counseled on the symptoms of increased ICP, including atypical headaches, pulsatile tinnitus, or transient visual obscuration, if being treated with a DIIH-associated medication in Categories III, IV, or V [1, 34]. It is recommended that clinicians perform a review of systems to rule out symptoms of elevated ICP when the patient is on DIIH-associated medications. Drugs most strongly associated with DIIH, such as vitamin A derivatives (especially isotretinoin) and tetracycline-class antibiotics, are commonly prescribed medications in dermatology; hence, dermatologists should be particularly cognizant about the risk of this uncommon ADR and maintain a high index of suspicion. If DIIH is suspected by the physician, a timely referral for co-evaluation and co-management by a neurologist and an ophthalmologist is recommended.

Online resources for patients are available on the Johns Hopkins Health Library (http://www.hopkinsmedicine.org/healthlibrary/) and the Intracranial Hypertension Research Foundation (ihrfoundation.org).

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Compliance with Ethical Standards

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