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Is routine laboratory testing in healthy young patients taking isotretinoin necessary: a critically appraised topic

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Summary

Clinical question Is monitoring of liver function, lipids and full blood count necessary in healthy people taking isotretinoin?

Background Routine blood testing was recommended in the original licence for Roaccutane™ (isotretinoin) in 1983. In recent years, less frequent monitoring has been suggested by various authors.

Data sources We performed four individual systematic searches of the MEDLINE database, via PubMed, from origin to 2 May 2021, supplemented by a hand search of all references in the identified papers.

Study selection Inclusion criteria were any description of clinical symptoms, laboratory abnormalities and/or physical findings, and any paper that explicitly described the patients as asymptomatic, during treatment with oral isotretinoin.

Data extraction Two independent reviewers (J.A. and D.J.) assessed articles for eligibility of inclusion. Evaluation of the data was done also by two of the authors (A.A., D.J. and J.A.) for each section, with the aim to use the presented evidence including guidelines, databases, case series, case reports, cohort studies and randomized clinical trials to delineate the clinical presentation and frequency of adverse events that might be amenable to laboratory monitoring.

Results We identified 407 papers in our searches and reviewed 125 papers in four sections. Overall, reported adverse events were very rare (< 1 in 10 000) and were either idiosyncratic or not preventable by monitoring, accompanied by symptoms, or seen in identifiable predisposed individuals who might benefit from monitoring because of pre-existing conditions.

Recommendation for clinical care We could not find evidence to support the benefit of monitoring to detect adverse events. We suggest that in healthy young people laboratory monitoring for oral isotretinoin is unnecessary and risks detecting nonserious biochemical abnormalities. However, we recognize that new information about adverse events may change that recommendation.

Clinical question

Is monitoring of liver function, lipids and full blood count (FBC) useful to detect serious adverse events in healthy people taking oral isotretinoin?

Clinical scenario

A 16-year-old healthy boy with no significant previous illnesses and severe treatment-resistant acne attends the dermatology clinic. He does not want to miss school and would like to forgo blood tests. Based on the available evidence can he be treated safely?

Background

Isotretinoin is a valuable acne treatment but remains controversial. It is the only treatment that can arrest severe acne permanently but causes a high frequency of birth defects or spontaneous abortions. It causes predictable elevation of liver

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function tests (LFTs) (see below), blood lipid elevations in around 20% of cases, and very rarely idiopathic pancreatitis. The British National Formulary (BNF) re-enforces concerns: 'Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist.'[1] Isotretinoin is the only generally toxic medication (i.e. not cardiotoxic, ototoxic etc.) in the BNF, with the exception of pentamine, that is classified as 'a potentially toxic drug'.[1] Even cyclophosphamide, a medication with a high-risk side-effect profile, does not have a similar warning.

Mitigation of adverse events is of the highest importance. The US Food and Drug Administration mandates a complex Risk Evaluation and Mitigation Strategy that has reduced the number of pregnancies on the drug by a third.[2]

In young healthy patients, expected changes of laboratory values can be challenging to interpret, and there is a large body of conflicting evidence.[3–6] Blood monitoring is not even mentioned in the recent guidelines from the National Institute for Health and Care Excellence.[7]

We wanted to investigate the clinical presentation of adverse events to understand whether laboratory monitoring prevents or detects adverse events early. We systematically searched and summarized the literature of evidence that laboratory monitoring is helpful, when it is helpful, and how often it should be done.

Aim of this critically appraised topic

To evaluate whether routine blood testing for liver function, lipids, FBC, thyroid function tests and muscle enzymes is needed in healthy people taking a course of isotretinoin for acne in order to prevent and act on adverse events. The approach is toxicological in that the observed adverse events are analysed clinically to assess whether laboratory monitoring can potentially prevent them, or whether early detection would lead to a change in outcome.

Methods

Identification of blood tests to be evaluated

The list of blood tests that are part of this critically appraised topic was based on discussions among the authors and *BJD* editorial teams.

Literature search

We limited the list of laboratory tests discussed in this critically appraised topic based on the package insert,[4] the BNF,[1] the British Association of Dermatologists (BAD) guidelines,[5] personal discussion and available literature. After discussion among the authors we focused on FBC, thyroid tests, liver enzymes, muscle enzymes and triglyceride checks.[8] These tests go beyond the package inserts and usual recommendations. We performed four individual systematic searches of the MEDLINE database, via PubMed, from origin to 2 May 2021, supplemented by a hand search of all references in the identified papers. The results for triglycerides were summarized based on a previous systematic review.[8] The searches with results and search terms are outlined in detail in Appendix S1 (see Supporting Information). All search results were independently selected for review by two reviewers (D.J., J.A.). Any differences of opinion were resolved by personal discussion.

Selection criteria

We screened articles based on their abstract and title. All relevant papers were reviewed in full text. Inclusion criteria were any description of clinical symptoms, laboratory abnormalities and/or physical findings, and any paper that explicitly described the patients as asymptomatic during treatment with oral isotretinoin. No restrictions were imposed on publication date, study design or language (excepting two papers in Hungarian and Hebrew where no translation could be found). Duplicate reports and articles that contained only abstracts were excluded (Figures S1–4; see Supporting Information).

Data extraction

A predetermined data form was used to extract information that included study design, sample size, and events with conclusions reported in the article.

Clinical approach

Analysis of rare events has to be clinical as statistical methods are not useful for exceedingly rare events. As a consequence case reports remain the basis for a majority of relevant safety decisions by regulatory agencies.[9–11] Monitoring has to be clinically sensible.

Drugs are removed from the market when the incidence of drug-induced liver injury (DILI) rises above 1 in 10 000.[12] Based on a simple rule,[13] a series of about 30 000 patients without events would be needed to show that the risk of DILI is below 1 in 10 000. Such large series are rare, so individual case reports have to be analysed. This was done for terbinafine, where the incidence of DILI is around 1 per 50 000–120 000 prescriptions, and 69 cases were analysed.[14] Based on clinical presentation, drug characteristics and reported frequency, an analysis of causal attribution and utility of monitoring can be made. In this way, our approach seeks to mimic that of agencies such as the Food and Drug Administration.

Liver function

Current recommendations

The BNF and Electronic Medicines Compendium (EMC) monitoring advice is to measure hepatic function before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase is persistently raised).[1,4] The

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Table 1 Types of studies and numbers of patients

Study type	No. of studies	No. of patients
Liver		
Case reports	9	9
Cohort studies – prospective	8	1408
Cohort studies – unclear or retrospective	28	23 358
Randomized controlled trials	6	397
Reviews or meta-analyses	10	NA
Haematology		
Case reports	11	11
Cohort studies – prospective	4	302
Cohort studies – unclear or retrospective	9	17 508
Reviews or meta-analyses	1	17 915
Thyroid		
Case reports	6	6
Cohort studies – prospective	6	233
Muscle		
Case reports	16	19
Cohort studies – prospective	1	89
Cohort studies – unclear or retrospective	4	1076
Controlled trial	4	1298
Reviews or meta-analyses	2	NA

NA, not applicable.

BAD guidelines recommend testing after 4–6 weeks, and then every 3 months.[5]

Evidence found

Our search identified 204 papers, of which 61 were selected for review; three additional papers were found in the references and three papers were excluded (Figure S1 and Table 1).

It is clear that isotretinoin leads to an elevation of liver enzymes in a large proportion of patients. We identified only one poorly documented case of 'probable' DILI,[15] based on the Council for the International Organization of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) criteria.[16,17] The CIOMS/RUCAM criteria are meant to assess causality in cases of hepatotoxicity. However, the paper does not give enough information to confirm 'probable' causation, only 'possible' causality. On day 70 of an isotretinoin course an asymptomatic female patient presented with elevated LFTs and bilirubin less than three times the upper limit of normal. The investigations to exclude other causes of liver injury are not documented, but this case fulfils the biochemical criteria for DILI.[18] The patient recovered fully.

One report linked autoimmune hepatitis in a patient with Hashimoto thyroiditis to isotretinoin after 3 months of therapy. Isotretinoin was stopped, steroids and azathioprine were initiated and the patient recovered.[19] The authors discuss isotretinoin, but fail to recognize the association of Hashimoto thyroiditis with autoimmune hepatitis. In one series, four of 46 patients with Hashimoto thyroiditis had autoimmune hepatitis.[20] No further cases of isotretinoin-associated autoimmune hepatitis were found.

A third patient developed mild derangement of liver enzymes on isotretinoin. After 4 months of therapy a biopsy found hepatosteatosis.[21] The patient had a low antitrypsin level, but no other underlying diseases that would explain the steatosis. The authors mention a similar case in the Roche database, although the investigations for this patient are not reported. Assessing causation is difficult, as hepatosteatosis is frequently found on biopsy of asymptomatic patients with liver enzyme elevation. In one series of 149 patients with moderately elevated transaminases, but not on isotretinoin, 64% of biopsied patients had fatty liver.[22] No other cases reporting this association with isotretinoin were found, and a case series of 50 patients did not show changes associated with isotretinoin.[23]

Interpretation

Following approval of isotretinoin in 1982, one case of probable DILI has been reported. Based on a single 'possible' event, it is possible, but not certain, that isotretinoin may cause DILI, and if it did it would appear to be extremely rare.[24] In the UK no death due to hepatobiliary disorders has ever been reported secondary to isotretinoin.[25] Isotretinoin certainly behaves differently from etretinate and acitretin and can be used in patients who have experienced liver injury due to these drugs.[24] Monitoring LFTs for drugs that cause DILI more commonly, like terbinafine,[14] is not useful,[12,14,26] and routine laboratory LFT monitoring for isotretinoin seems to be similarly unhelpful. Instead, informing the patient about the potential symptoms of DILI would be more appropriate. If symptoms of DILI (e.g. dark urine, abdominal pain, generalized itch or jaundice) arise, LFTs need to be checked and isotretinoin withheld until investigations have been concluded.

It should be noted that asymptomatic DILI, even if it crosses the threshold of laboratory diagnosis, may resolve on continuing therapy.[12,26] Adaptation is a transient increase in liver enzymes, but by definition does not progress to DILI and is not clinically relevant. This is what we commonly see in patients receiving isotretinoin.[12,26,27] McElwee *et al.* report a patient with a baseline aspartate transaminase level of 41 U L^{-1}, which increased to 235 U L^{-1} after 7 days of therapy only to normalize thereafter on continued therapy.[28] Given the available data, we believe that isotretinoin behaves similarly to other drugs like aspirin and heparin that increase liver enzymes without causing DILI.[12]

The data presented do not suggest that baseline monitoring is helpful, particularly in younger healthy patients. Blood tests will be likely to find spurious elevations that may be irrelevant, but need further investigation.[29,30] The level of abnormality is not necessarily a guide to clinical significance,[29,30] and is independent of the likelihood of isotretinoin-associated DILI. Given the age group it should be noted that activities like weightlifting lead to increases in liver enzymes for at least a week,[31] and that muscular diseases like limb-girdle muscular dystrophy may present only with elevation of liver enzymes as a reflection of muscle damage.[32]

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Lipids

Current recommendations

The BNF and EMC recommend measuring serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if serum lipids are persistently raised).[1,4] The BAD guidelines recommend additional fasting lipids at 4–6 weeks and then repeat tests every 3 months.[5]

Interpretation

Lipid abnormalities were the subject of a review from 2016 that followed the format and methodology of a critically appraised topic.[8] Isotretinoin reliably increased triglyceride levels by 20–40% and reduced high-density lipids. Due to the brevity of treatment this is unlikely to increase cardiovascular risk.[33] Hypertriglyceridaemia-associated pancreatitis is an exceedingly rare adverse event with isotretinoin, which is now thought not to occur in patients with fasting triglycerides < 2000 mg dL^{-1} (22·6 mmol L^{-1}).[34] The drug information for isotretinoin may be explained by the outdated lower triglyceride threshold for pancreatitis when the label was developed.[4,8] Triglyceride-induced pancreatitis has only been reported in three patients, who were older than 35 years and had elevated triglycerides at baseline. A fourth patient was part of a glioblastoma trial and further information is not available. None of the patients was monitored. Idiosyncratic pancreatitis due to isotretinoin is a very rare but real adverse event.[35] It is poorly understood, but more frequent than hypertriglyceridaemia-associated pancreatitis. Patients need to be warned.[35]

Triglyceride-induced pancreatitis for younger patients is virtually nonexistent (i.e. has never been reported), thus baseline triglyceride monitoring is unnecessary for typical teenagers if they have no other risk factors for elevated triglycerides.[36–38]

It is appropriate to check baseline triglycerides in those who have risk factors for elevated triglycerides based on truncal obesity, family and personal history, or signs of insulin resistance, like acanthosis nigricans.[39–41] These patients could have their fasting triglycerides checked after 4 weeks of therapy. If they are not significantly elevated, no further monitoring is warranted.

Monitoring of triglycerides after 2 months has no utility,[8,36,42,43] unless the isotretinoin dosage is changed. The exception is high-risk patients, where treatment interruption, dose reduction and diet intervention,[44] possibly even fibrates, may be necessary – these patients are rare exceptions and can be identified at the beginning of their therapy.[8]

Full blood count

Current recommendations

According to the BNF and EMC, FBC monitoring is not recommended.[1,4] The BAD guidelines recommend FBC before treatment, at 4–6 weeks and then every 3 months.[5]

Evidence found

In total, 84 papers were identified, and 25 were included for review (Figure S2 and Table 1). This review includes 13 clinical studies and one review with a total of 17 915 patients. Mild changes in FBC were noted in several studies, and in the package insert;[4] however, none reached clinically significant levels. Seven groups concluded that routine FBC monitoring was unlikely to be of clinical use, due to the rarity of significant abnormalities.[36,43,45–49]

Eleven case reports were identified that discussed haematological abnormalities in patients taking oral isotretinoin. There were three cases of agranulocytosis or neutropenia. In two cases isotretinoin was felt to be the probable trigger;[50,51] however, in the third case the patient displayed an ongoing mild neutropenia for 30 weeks despite drug cessation, suggesting that benign ethnic neutropenia or cyclical neutropenia may be more likely.[52]

Two cases of thrombocytopenia were noted in the literature. In one case the patient had also received cephalexin; however, isotretinoin was deemed more likely given the prolonged duration of the thrombocytopenia.[53] In the second case, rechallenge confirmed isotretinoin as a cause.[54]

Anaemia is often listed as a common side-effect in the product information;[4] however, about 10% of women in the USA have iron-deficiency anaemia.[55] Iron-deficiency anaemia can be associated with nodular cystic acne and may improve following treatment with isotretinoin.[56] One case of B12/folate-deficient anaemia was identified during a course of isotretinoin, after the patient developed colitis.[57] However, given that no prior FBC monitoring was performed it is difficult to be certain whether a pre-existing deficiency was unmasked by isotretinoin, rather than driven by it.

Interpretation

Mild haematological abnormalities are common in patients on isotretinoin. However, of 17 915 patients enrolled in a range of clinical studies in this review, no serious adverse drug reactions were noted on FBC monitoring.

Based on case reports, there are two probable cases of isotretinoin-induced neutropenia, and two of thrombocytopenia. It is reassuring to note that isotretinoin was not identified in a multinational study of drug-induced agranulocytosis and it is not considered a drug of high risk.[58] It is likely that the risk of agranulocytosis is lower than the 0·6 cases per 1 million users per week that was found for doxycycline.[58] To evaluate such rare events, one would likely need a cohort study sized in the 100 000s or perhaps even millions for stable estimates. The question then is whether quantification is necessary for adverse events that are rare and not amenable to prevention, or indeed early detection, such as thrombocytopenia, given that the half-life of thrombocytes is 7–10 days. Given this degree of rarity, routine monitoring is no longer recommended by either the BNF[1] or the EMC[4] (although it is still referred to in the BAD guidelines from 2010).[5]

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However, sepsis develops rapidly in the setting of agranulocytosis, and thus it may be prudent to warn patients of symptoms of blood dyscrasias (e.g. sore throat, fever, severe malaise) rather than to monitor blood at monthly intervals. For dapsone, even weekly monitoring has been insufficient to prevent lethal agranulocytosis-induced sepsis, and dapsone, or even terbinafine, has more reports of agranulocytosis than isotretinoin has.[59] In addition no death due to haematological disorders has been reported in the UK.[25]

Thyroid function tests

Current recommendations

No monitoring is recommended. Thyroid function abnormalities are not listed as adverse events.[1,4,5]

Evidence found

Forty-five papers were identified from our PubMed search, of which 11 were retrieved; one was excluded as being irrelevant based on the full text and two more were found based on references (Figure S3 and Table 1).

Interpretation

Bexarotene is a related retinoid and highly specific for retinoid X receptors. It is well known to cause central hypothyroidism, but isotretinoin has not shown this affinity. Thyroid abnormalities secondary to isotretinoin have been reported since the 1980s,[60–65] but the number of cases is small, and no pattern of timeline or abnormalities has emerged to support causation. Since the 1980s prospective cohort studies have followed patients receiving isotretinoin to investigate the influence of isotretinoin on hormonal homeostasis.[48,65–69] Some of these studies found mild changes of thyroid hormones, but none was clinically significant. National guidelines in the USA[70] and the UK[71] do not recommend screening for thyroid disease in asymptomatic patients. Since 1983, 19 cases of endocrine disorders not further specified have been reported in the UK, none lethal.[25] In summary, thyroid test screening in patients on isotretinoin is likely to be unnecessary in the asymptomatic.

Musculoskeletal

Current recommendations

No monitoring is recommended. Myalgia, arthralgia and rhabdomyolysis are listed as side-effects.[1,4] The BAD guidelines do not recommend monitoring but note that myalgia, arthralgia and increased serum creatine phosphokinase (CK) values have been reported in those undertaking vigorous physical activity, with risk of progression to potentially life-threatening rhabdomyolysis.[5]

Evidence found

In total, 74 papers were identified from our PubMed search, of which 27 were included for review (Figure S4 and Table 1).

Isotretinoin has been associated with a range of musculoskeletal side-effects, including precipitation of acne fulminans, arthralgia, Achilles tendonitis,[72] myalgia without CK elevation, and hyperCKaemia, both with and without development of rhabdomyolysis.[47,73–82]

Myalgia and mild transient elevations in CK are common, and were observed in 20% of patients in a small series.[47] Significant elevations are much less frequent, with Manfredini *et al.*[73] detecting CK over five times the upper reference range in 1·2% of patients, and Landau *et al.*[81] noting CK > 5000 IU L^{-1} in 1·6% of patients (although Landau's was a military population). Multiple factors can influence CK including ethnicity, age, sex and physical activity.[83] The relevance of these elevations in CK remains disputed. Transient elevations of CK with exercise are common in young fit individuals, with Kenney *et al.* noting levels as high as 35 056 IU L^{-1} in healthy training military recruits.[84] Without other aggravating factors such as sepsis, dehydration or acidosis, the risk of acute kidney injury in rhabdomyolysis is much lower in patients with CK levels < 15 to 20 000 IU L^{-1}.[85] Indeed, clinical trials generally define statin myotoxicity as myalgia with CK elevation over 10 times the upper reference limit.[86] Thus in young healthy patients, even relatively high CK levels (over five times the upper reference range) are unlikely to precipitate rhabdomyolysis.

It should also be noted that elevations in CK do not always correlate with symptoms of myalgia; in the study of Landau *et al.*, of eight patients with a CK above 5000 IU L^{-1}, only two were symptomatic.[81] Conversely, severe myalgia with significant proximal weakness or stiffness has been reported with minimal change in CK levels,[78,87] although there may be a role for L-carnitine in these symptoms.[88] Our literature review identified eight cases of rhabdomyolysis secondary to isotretinoin,[74–76,79,80,82,89,90] with one fatality.[79] This has occurred with as little as 20-mg daily dosing, although patients often note recent vigorous exercise as a potential trigger.

Interpretation

While the incidence of rhabdomyolysis is unknown, given the paucity of case reports it is likely to be rare, but not unheard of. In the UK about 500 cases of musculoskeletal disorders have been reported since 1983, that is about 12 per year, none of them lethal.[25] If these cases are rapidly precipitated by vigorous exercise, routine CK monitoring is likely to be ineffective. Education regarding limiting vigorous physical activity and identifying clinical symptoms of rhabdomyolysis (fatigue, myalgia and myoglobinuria) are a more effective strategy. For statin therapy, rhabdomyolysis is a significant problem. The lipid expert panel has developed algorithms for

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athletes that suggest therapy breaks, dose adjustment or therapy changes based on CK results.[91] These cannot be applied directly to isotretinoin, but the approach may be helpful in selected cases.

Limitations

This review used published data of adverse events and thus will only identify a small subset of cases that have occurred; for the UK the estimate is that the yellow card system only identifies 10% of all serious adverse events.[92]

Isotretinoin has been on the market for nearly 40 years, and based on usage data from 2013 to 2019 we estimate that isotretinoin has been prescribed in the USA alone to at least 10 million patients.[93] In the UK none of the organ systems discussed have been associated with death in the yellow card system, which confirms the literature as presented.[25]

The interest in adverse effects of isotretinoin has been substantial since marketing began, and consequently the literature is very broad and has included reports of associations that are most probably coincidental, and over the 40 years have not been observed again.

While none of the cohort studies included was powered to identify very rare adverse events, given the number of papers and cohort studies we are optimistic that the range of adverse events that we identified is representative. In addition we have limited the scope of this review purely to the question of routine laboratory monitoring, and whether the clinical characteristics of the reported adverse events meant that they can be detected and prevented with laboratory tests. The frequency of these events and pharmacoeconomic analysis can only be estimated with exact data, which we do not have.

Discussion and clinical message

Our review could not identify a single blood test that seems reasonable to perform routinely, given the rarity of the adverse outcomes identified in the literature in healthy young patients, or the rapidity of their clinical development. While more systematic research is always desirable, this would have to be population wide for large countries, or the European Union, to accurately detect and quantify adverse events for isotretinoin. However, 40 years after market introduction the description of rare events that may change this recommendation is unlikely.

Rather than being routine, we believe that blood tests need to be individualized based on risk factors. Patients with significant obesity, acanthosis nigricans, diabetes or a history of significant hypertriglyceridaemia may benefit from measurement of baseline triglycerides, but the overwhelming majority will never reach the fasting 2000 mg dL^{-1} that would put them at risk for pancreatitis.

LFTs will frequently be elevated on isotretinoin but the risk of DILI is negligible, if it even exists, and routine monitoring is not helpful. Minor cell death is part of liver adaptation to various drugs. The liver is resilient and has enormous repair capacity. It tolerates up to 70% resection[94] and living partial liver donors expect factors such as coagulation abnormalities to resolve in 1–2 weeks.[95]

Patients need to be informed about isotretinoin's rare adverse events, particularly pancreatitis and rhabdomyolysis, so they are aware of the need to present should symptoms develop.

However, our findings suggest that routine monitoring may be falsely reassuring without improving safety. It is likely to be driving overinvestigation of spurious results, generating avoidable healthcare costs, and causing confusion and anxiety until results are correctly evaluated. It should also be noted that the adverse events we identified in this review are considered so irrelevant that regulatory agencies have not found it necessary to react with package insert amendments, or black box warnings. We agree with that assessment.

Clinical scenario

We treated the patient with isotretinoin without laboratory monitoring. He was counselled on symptoms that should prompt laboratory evaluation, but remained well throughout the course with resolution of his acne and mild dry skin and cheilitis.

Funding sources

None.

Conflicts of interest

J.A. is an investigator for Medpace and Biogen. The other authors declare they have no conflicts of interest.

Data availability

The data are available on request from the authors.

Ethics statement

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Search strings.
Figure S1 Liver PRISMA flowchart.
Figure S2 Complete blood count PRISMA flowchart.
Figure S3 Thyroid function PRISMA flowchart.
Figure S4 Musculoskeletal PRISMA flowchart.

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