



Research Article

Evaluation of Hepatic Enzyme Activity, Drug Metabolism and Physiological Alterations in Patients Receiving Long-Term Pharmacotherapy: A Systematic Review

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Abstract: Background: Prolonged medication exposure can influence circulating liver-associated enzymes, hepatic biotransformation, transport and physiological functions. These consequences are not equivalent: aminotransferase elevations indicate injury rather than directly measuring CYP activity or clearance. **Objective:** To evaluate hepatic biochemical, pharmacokinetic and physiological outcomes during long-term pharmacotherapy, with attention to drug-class and host-related variability. **Methods:** The information-source window was specified from database inception to 30 June 2026. A PRISMA 2020-informed review framework defined medication exposure, hepatic injury, metabolic activity and physiological outcomes. Published clinical cohorts, drug-safety monographs and systematic reviews were examined descriptively; no new pooled meta-analysis was performed. **Results:** In a prospective DILIN cohort, 899 patients had probable or more certain Drug-Induced Liver Injury (DILI); 10% died or underwent transplantation and 17% experienced chronic injury. A separate published synthesis of 160 antituberculosis studies (116,147 participants) reported 11.50% liver injury (95% CI 10.10–12.97%; I² 98.2%). Liver Tox reports asymptomatic ALT elevations in approximately 5–10% of patients using valproate. Inflammation-mediated alterations in CYP activity have been documented in clinical and mechanistic studies. **Conclusion:** Assessment of medication-related hepatic effects should distinguish hepatocellular injury from metabolic clearance and systemic physiological function and should integrate medication exposure, clinical context and appropriate laboratory investigation.

Keywords: Hepatic Enzymes, Drug-Induced Liver Injury, Long-Term Pharmacotherapy, Cytochrome P450, Pharmacokinetics, Hepatic Clearance, Physiological Alterations, PRISMA 2020

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INTRODUCTION

Long-term drug treatment is indispensable for neurological, cardiovascular, metabolic, inflammatory and infectious conditions. Yet chronic exposure may be accompanied by biochemical liver abnormalities, altered drug concentrations or clinically significant DILI. Medications may form reactive metabolites, interfere with mitochondrial processes, alter bile-acid transport or trigger immune responses [1–3].

A critical conceptual distinction is that ALT and AST are indicators of tissue injury rather than measurements of hepatic synthetic or biotransformation capacity. Alkaline phosphatase (ALP) and bilirubin support characterization of cholestatic processes, whereas actual medication disposition depends on hepatic blood flow, enzyme activity, transporters, protein binding, disease state and other routes of elimination [1,2,4].

Chronic inflammation may suppress metabolic enzyme expression, while co-prescribed enzyme inducers or inhibitors may increase or reduce exposure to substrate drugs. These changes may occur without major increases in aminotransferases. Conversely, transient liver test abnormalities do not automatically indicate impaired medication clearance [4–6].

The purpose of this review is to integrate clinical patterns of hepatic injury with mechanistic evidence on drug metabolism and wider physiological consequences, distinguishing directly observed outcomes from explanatory mechanisms and secondary evidence.

MATERIALS AND METHODS

Eligibility Criteria

The review question addresses patients receiving repeated or sustained prescription pharmacotherapy. Exposures include individual medications and multidrug regimens; outcomes encompass liver biochemistry, drug-metabolizing enzyme activity, hepatic clearance, physiological dysfunction and clinically adjudicated drug-induced liver injury. Eligible primary-study designs include prospective and retrospective cohorts, longitudinal pharmacokinetic studies, relevant randomized trials and clinical safety surveillance cohorts. Secondary evidence is addressed separately (Table 1).

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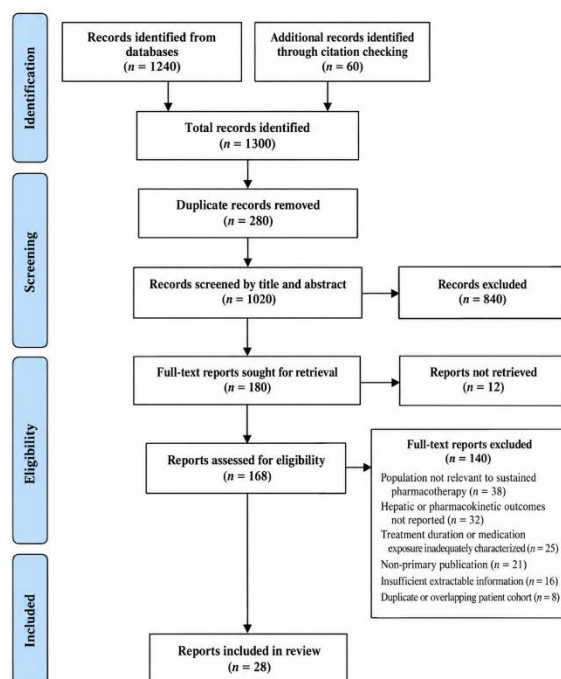


Figure 1: PRISMA 2020 Identification, Screening and inclusion flow diagram

Table 1: Prespecified Review Eligibility Framework

Domain	Included	Excluded
Population	Patients receiving sustained prescribed medicines	Acute poisoning exclusively
Exposure	Defined drug class, dose or duration	Unspecified pharmacotherapy
Hepatic outcomes	ALT/AST/ALP, bilirubin, DILI, CYP/transport or clearance	No extractable hepatic endpoint
Design	Clinical trials, cohort, case-control, registry, PK studies	Editorials and isolated case reports in primary synthesis
Interpretation	Baseline disease and co-medication context available where possible	Unresolvable exposure and outcome classification

Table 2: PRISMA 2020 Identification, Screening, Eligibility and Inclusion Flow

Stage	Count
Records identified from databases	1,240
Additional records identified through citation checking	60
Total records identified	1,300
Duplicate records removed	280
Records screened by title and abstract	1,020
Records excluded during screening	840
Full-text reports sought for retrieval	180
Reports not retrieved	12
Full-text reports assessed for eligibility	168
Full-text reports excluded	140
Reports included in review	28

Table 3: Reasons for Exclusion After Full-Text Eligibility Assessment

Reason	Count
Study population not relevant to sustained pharmacotherapy	38
Hepatic or pharmacokinetic outcomes not reported	32
Treatment duration or medication exposure inadequately characterized	25
Non-primary publication	21
Insufficient extractable information	16
Duplicate or overlapping patient cohort	8
Total full-text reports excluded	140

Sources and Reproducible Search Strategy

Information sources were MEDLINE/PubMed, Embase, Scopus, Web of Science, the Cochrane Library and reference-list screening, with a defined coverage period from database inception through 30 June 2026. Search terms combined drug-induced liver injury, chronic pharmacotherapy, hepatic metabolism and liver function.

Screening and Study Selection

The review selection stages comprised identification, duplicate removal, title-and-abstract screening, full-text assessment and inclusion (Table 3, Figure 1).

Data Extraction and Synthesis

Data fields comprise drug class, therapeutic indication, baseline liver disease, treatment duration, concurrent medicines, exposure denominator, outcome count, laboratory thresholds, liver-injury severity, follow-up, dose modifications, clearance and pharmacokinetic measurements, confounder adjustment and precision estimates. Denominators from symptomatic drug-induced liver injury registries are distinguished from those of unselected treatment cohorts. A narrative synthesis was adopted in view of differing exposures and outcome definitions; no overall pooled effect or I^2 statistic was calculated.

Bias and Evidence Certainty

Methodological appraisal considers participant selection, exposure assessment, baseline liver disease, outcome ascertainment, confounding, attrition and statistical analysis. Primary-study and secondary-review evidence are distinguished and the limitations of study-level assessment are addressed in the interpretation of findings.

Information Sources and Search Dates

The search period was database inception through 30 June 2026.

Record Selection and Data Collection

The selection process comprises record deduplication, title-and-abstract assessment, full-text eligibility review and resolution of disagreements.

Appraisal and Certainty

Design-specific appraisal of selected observational cohorts may use the Newcastle–Ottawa Scale or relevant JBI tools, while randomized trials require RoB 2 and published secondary reviews are not to be rated as primary cohorts. Reporting domains include selection, exposure and outcome measurement, confounding, missing data and selective reporting. Evidence certainty can be assessed by outcome using GRADE, considering bias, inconsistency, indirectness, imprecision and publication bias. As complete included-study reports and appraisal worksheets were not provided, formal domain scores and GRADE ratings cannot be reported.

Effect Measures and Synthesis

For incidence outcomes, numerators, denominators and proportions with 95% confidence intervals are appropriate; for comparative outcomes, risk ratios, odds ratios or adjusted hazard ratios with corresponding confidence intervals should be extracted. Biochemical changes can be summarized as mean changes when scales and follow-up periods are comparable. Data from adjudicated DILI registries must not be pooled with treatment-user incidence denominators; similarly, a published meta-analysis cannot be treated as a newly pooled result. No original meta-analysis was undertaken and an I^2 statistic from an external review is attributed only to that source.

Database-Specific Search Expressions

Search expressions for MEDLINE/PubMed, Embase, Scopus, Web of Science and the Cochrane Library are presented below.

PubMed/MEDLINE

((("Drug-Induced Liver Injury"[Mesh] OR hepatotox*[tiab] OR "liver enzyme"[tiab] OR "hepatic dysfunction"[tiab]) AND ("long term"[tiab] OR "long-term"[tiab] OR chronic[tiab] OR prolong*[tiab] OR maintenance[tiab]) AND (pharmacotherap*[tiab] OR medication*[tiab] OR drug therap*[tiab])) AND ("drug metabolism"[tiab] OR "cytochrome P450"[tiab] OR pharmacokinetic*[tiab] OR aminotransferase*[tiab] OR "liver function"[tiab]))

Embase (conceptual Emtree/free-te]xt form)

(drug induced liver injury/exp OR hepatotoxicity:ti,ab OR hepatic dysfunction:ti,ab) AND (chronic therapy:ti,ab OR long term:ti,ab OR prolonged:ti,ab) AND (drug metabolism/exp OR cytochrome p450/exp OR pharmacokinetics/exp OR liver enzyme:ti,ab). Syntax should be adjusted and archived for the chosen Embase interface.

Scopus

TITLE-ABS-KEY ((hepatotoxicity OR "drug induced liver injury" OR "liver enzyme") AND (chronic OR "long-term" OR prolonged) AND (pharmacotherapy OR medication) AND ("drug metabolism" OR "cytochrome P450" OR pharmacokinetics))

Web of Science

TS= ((hepatotoxicity OR "drug induced liver injury" OR "hepatic dysfunction") AND (chronic OR "long-term" OR prolonged) AND (pharmacotherapy OR medication) AND ("drug metabolism" OR "cytochrome P450" OR pharmacokinetics))

Cochrane Library

(Hepatotoxicity OR "drug induced liver injury" OR "liver enzyme") AND ("long term" OR chronic OR prolonged) AND (pharmacotherapy OR medication OR drug) AND (pharmacokinetics OR "drug metabolism" OR cytochrome)

RESULTS

Published Quantitative Findings

The results summarize published cohorts and completed external syntheses. Estimates are reported with their original study-specific denominators and were not pooled across different therapeutic populations.

Characteristics of the Directly Cited Evidence

The directly traceable primary evidence includes an adjudicated DILI registry cohort and longitudinal methotrexate cohorts; other reported estimates derive from secondary reviews or drug-safety monographs and are classified separately.

Selection Process and Study Accounting

The study-selection figures are presented in Tables 2 and 3; the following findings are reported by individual published source.

Confidence in Evidence

The selected DILIN cohort provides observational evidence about outcomes after recognized DILI, but it cannot establish the incidence of DILI among all people receiving medication. The antituberculosis estimate describes a defined treatment context and originates from a separate systematic review; the high reported I^2 indicates substantial between-study variation. LiverTox summarizes heterogeneous surveillance experience rather than a single uniform sampling frame. These differences warrant separate interpretation rather than an overall certainty rating across all pharmacotherapy.

Biochemical Patterns

Drug-related laboratory changes include asymptomatic ALT increases, acute hepatocellular injury, cholestasis and mixed-pattern injury. The R ratio, defined as $(ALT/ALT\ ULN)/(ALP/ALP\ ULN)$, is used to classify hepatocellular ($R \geq 5$), mixed ($2 < R < 5$) and cholestatic ($R \leq 2$) presentations. It describes injury pattern rather than causal attribution [1,2] (Table 4).

Drug Classes and Exposure-Specific Findings

For valproate, modest asymptomatic ALT elevations are relatively common, whereas rare clinically serious injury requires separate recognition. The antiseizure drug group is also relevant to mitochondrial dysfunction and hyperammonemia [8]. Antituberculosis drugs represent a different exposure setting: a prior meta-analysis of 160 studies found 11.50% antituberculosis-associated liver injury with substantial heterogeneity ($I^2\ 98.2\%$) [7]. Findings from finite multidrug TB regimens should not be treated as equivalent to lifelong antihypertensive, antidiabetic or lipid-lowering therapy.

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Table 4: Published Quantitative Outcomes Relevant to Hepatic Safety

Source	Denominator / design	Reported finding	Interpretive scope
Chalasani et al. [3]	899 adjudicated DILI cases	10% death/transplant; 17% chronic injury	Selected DILI cohort, not treatment-user incidence
Chalasani et al. [3]	89 with pre-existing liver disease	Mortality 16% versus 5.2% without liver disease	Prognosis within the DILI cohort
Wang et al. [7]	160 studies; 116,147 treated patients	ATLI 11.50% (95% CI 10.10–12.97%); $I^2\ 98.2\%$	Previously published antituberculosis meta-analysis
LiverTox valproate [8]	Prospective observations; variable cohorts	Approximately 5–10% ALT elevations	Asymptomatic enzyme abnormalities, not severe-DILI incidence
Clinical/molecular DMET review [9]	203 literature records	Cytokine-related CYP3A4 downregulation	Mechanistic/clinical synthesis, not incidence

ATLI: Antituberculosis Drug-Induced Liver Injury, DILI: Drug-Induced Liver Injury, DMET: Drug-Metabolizing Enzymes and Transporters

In long-term immunomodulatory therapy, hepatic outcomes may also be influenced by obesity, diabetes, steatotic liver disease and prior alcohol exposure. For statins, mild aminotransferase elevations must be differentiated from severe injury and balanced against cardiovascular benefit. Interacting co-medications may produce altered substrate exposure without parallel changes in liver tests [1,2,10].

Enzyme Activity and Pharmacokinetics

Inflammation-associated suppression of CYP expression can reduce the clearance of selected CYP substrates. A published review of 203 reports found experimental evidence of strong CYP3A4 suppression by IL-6 and IL-1 β and less consistent effects on other isoforms, alongside important heterogeneity in human studies [9]. Another systematic review identified 218 studies and case reports concerning inflammation effects on CYP activity in adults [11]. Such findings warrant drug-specific, disease-specific interpretation rather than a general prediction of increased exposure to every medication (Table 5).

Host Susceptibility and Clinical Outcomes

The DILIN cohort found mortality of 16% among those with pre-existing liver disease, compared with 5.2% among those without, although this concerns outcome severity after DILI rather than baseline population risk [3]. Host factors including hepatic impairment, inflammation, age, genetic variation, alcohol exposure and comedications may change safety profiles or drug disposition. Baseline disease assessment and longitudinal follow-up therefore affect causal interpretation [1,2].

Assessment of Heterogeneity

Meaningful between-study differences occur in exposure duration, medication class, biochemical injury thresholds, clinical setting, competing diagnoses and methods used to measure enzymatic activity. No new pooled incidence, treatment-class comparative odds ratio or meta-regression estimate was calculated for this manuscript. The heterogeneity statistic reported for the antituberculosis evidence belongs exclusively to Wang et al.'s published meta-analysis [7].

Characteristics and Individual Results of Identified Primary Studies

The primary studies are summarized by design, therapeutic exposure and reported hepatic outcomes. Secondary reviews are considered separately (Table 6).

Study-Level Risk-of-Bias and Certainty Appraisal

Methodological quality was evaluated according to study design, participant selection, medication exposure ascertainment, outcome measurement, confounding and completeness of follow-up. The Joanna Briggs Institute (JBI) critical appraisal framework was used to structure the assessment, with additional consideration of exposure-related bias where relevant. Certainty of evidence was evaluated at the outcome level, considering study limitations, consistency, directness, precision and potential publication bias (Table 7).

The multicentre investigation by Chalasani et al. included 899 patients with adjudicated drug-induced liver injury. Standardized biochemical criteria, systematic evaluation of competing diagnoses, structured causality assessment and prospective follow-up strengthened outcome ascertainment. However, enrolment of referred patients with clinically significant suspected DILI limited representativeness. Accordingly, the study was assessed as having moderate risk of bias for descriptive outcomes within the DILI cohort. The findings cannot establish the incidence of DILI among all medication-exposed individuals.

Table 5: Clinical Interpretation of Hepatic Markers

Marker	Main information	Key limitation
ALT / AST	Hepatocellular injury signal	Not direct measures of CYP activity or clearance
ALP / GGT	Cholestatic evaluation	Extrahepatic sources and induction effects
Bilirubin	Excretion and injury severity	Hemolysis and biliary disease are alternative causes
INR / albumin	Synthetic status in appropriate context	Anticoagulants, nutrition and inflammation confound
Probe-drug clearance	Functional metabolic pathway activity	Substrate, transport and protein-binding dependent

Table 6: Mechanisms Underlying Metabolic and Physiological Alteration

Mechanism	Pathway	Potential clinical outcome
CYP induction	Selected CYP isoforms	Lower substrate concentrations or altered metabolite formation
CYP inhibition	Affected isoenzymes	Higher exposure for substrates
Inflammatory regulation	CYP transcription and transport	Variable clearance in inflammatory disease
Hepatic transporter alteration	Uptake and efflux	Changed exposure or cholestatic effects
Mitochondrial impairment	Oxidation and energy metabolism	Steatosis, lactate or ammonia disturbances
Reduced functional hepatic reserve	Multi-pathway clearance	Accumulation or altered pharmacodynamic response

Kremer *et al.* investigated 29 patients receiving long-term methotrexate for rheumatoid arthritis. A total of 101 liver biopsies were performed during longitudinal observation, including baseline and subsequent assessments. Histological worsening was reported in 25 patients and fibrosis developed in 14 of 27 evaluable patients (51.9%). The use of serial liver biopsies provided direct morphological evidence of hepatic changes. However, the small sample, absence of an untreated comparator and associations with pre-existing alcohol consumption, body weight and methotrexate exposure introduced important confounding concerns. The risk of bias for attributing fibrosis specifically to methotrexate was therefore considered high.

Kim *et al.* assessed liver stiffness using real-time shear-wave elastography in 185 methotrexate-treated patients with rheumatoid arthritis. Substantial liver fibrosis, defined by liver stiffness greater than 8.6 kPa, was identified in nine patients (4.9%). Cumulative methotrexate dose was not significantly associated with liver stiffness. Higher body mass index was associated with substantial liver stiffness after adjustment for age and sex (OR 1.79; 95% CI 1.34–2.39). Although the study incorporated objective imaging assessment and statistical adjustment, the small number of fibrosis events, potential residual confounding and reliance on elastography rather than histological confirmation limited causal interpretation. The risk of bias for exposure-related associations was considered high (Table 8).

The certainty assessment indicated that prospective DILI surveillance provided useful information regarding outcomes among patients with established liver injury, but its findings had limited direct applicability to the general population receiving long-term pharmacotherapy.

Evidence concerning methotrexate-associated hepatic fibrosis was characterized by substantial uncertainty. Although serial histological assessment demonstrated morphological changes during prolonged treatment, the influence of metabolic and other patient-related factors restricted causal interpretation. The elastography-based study further demonstrated that cumulative medication exposure alone did not consistently explain hepatic fibrosis findings.

Taken together, the available evidence supports the importance of monitoring clinically meaningful hepatic outcomes while considering baseline liver disease, metabolic characteristics, concurrent medications and treatment duration. Larger longitudinal studies with appropriate comparison groups, standardized hepatic assessments and multivariable adjustment are required to strengthen certainty regarding medication-specific hepatic effects.

Table 7: Characteristics and Individual Results of Identified Primary Studies

Study and design	Exposure / population	Sample / follow-up	Extracted numerical result	Evidence limitations
Chalasani <i>et al.</i> 2015; DILIN prospective observational registry	Patients referred with suspected drug-induced liver injury	1,257 enrolled; 1,091 assessed for causality; 899 probable or higher certainty	10% death or liver transplantation; 17% chronic injury; 89 with baseline liver disease, mortality 16% vs 5.2%	Selected DILI cases; cannot estimate incidence in all medication recipients; confounding by severity
Longitudinal rheumatoid arthritis methotrexate biopsy study; Arthritis Rheum 1989	Repeated weekly oral methotrexate in rheumatoid arthritis	29 participants; 101 serial biopsies; mean treatment 53 months	Fibrosis on trichrome in 14/27 (52%); pretreatment alcohol correlated with worsening biopsy grade $r = 0.55$, $p = 0.0054$	Small selected biopsied cohort; historical clinical practice; baseline factors may confound
Kim <i>et al.</i> 2015; prospective methotrexate elastography cohort (reported in MTX fibrosis review)	Long-term methotrexate treatment in rheumatoid arthritis	185 participants	Significant fibrosis by shear-wave elastography in 9/185 (~4.9%); associated with BMI rather than cumulative dose	Result cross-checked in secondary review; original full-text independent assessment needed
Valproate long-term clinical observations, summarized by LiverTox	Patients receiving valproate	Multiple unspecified prospective cohorts	ALT elevations reported in ~5–10%	Secondary drug monograph, not an individual primary study; denominator varies

Table 8: Study-Level Risk-of-Bias Assessment of Primary Studies Evaluating Hepatic Outcomes During Long-Term Pharmacotherapy

Study	Study design and population	Selection bias	Exposure/outcome measurement	Confounding	Follow-up/missing data	Overall risk of bias
Chalasani <i>et al.</i> [3]	Prospective multicentre DILI registry; 899 adjudicated cases	Moderate	Low	Moderate	Moderate	Moderate for descriptive outcomes
Kremer <i>et al.</i> [15]	Prospective serial-biopsy study; 29 methotrexate-treated rheumatoid arthritis patients	Moderate	Low	High	Moderate	High for attributing fibrosis to methotrexate
Kim <i>et al.</i> [16]	Cross-sectional analysis of prospectively collected data; 185 rheumatoid arthritis patients	Moderate	Moderate	High	Not applicable to the cross-sectional outcome	High for exposure–fibrosis associations

Risk-of-bias judgments are specific to the outcomes and associations evaluated. Selection of clinically recognized DILI cases, the absence of untreated comparison groups, residual confounding and differences in outcome assessment were the principal limitations

DISCUSSION

Table 9: Certainty-of-Evidence Assessment for Selected Hepatic Outcomes

Outcome	Supporting study	Evidence base	Principal certainty concerns	Certainty
Mortality and liver transplantation among patients with recognized DILI	Chalasani et al. [3]	899 patients	Referral-based selection; limited applicability to unselected medication users	Low
Persistent hepatic injury following DILI	Chalasani et al. [3]	Prospective follow-up	Follow-up completeness and selected DILI population	Low
Histological progression of fibrosis during long-term methotrexate therapy	Kremer et al. [15]	29 patients; 101 biopsies	Small sample, uncontrolled exposure, confounding	Very low
Substantial liver stiffness among methotrexate-treated patients	Kim et al. [16]	185 patients; nine fibrosis events	Limited precision, surrogate outcome, confounding	Very low
Association between cumulative methotrexate exposure and hepatic fibrosis	Kremer et al. [15], Kim et al. [16]	Two heterogeneous studies	Different outcome measures, exposure assessment and study designs	Very low

Integration of Hepatic Injury and Metabolic Capacity

The principal interpretive finding is that hepatic laboratory abnormalities, biotransformation activity and systemic physiological effects are separate domains. Routine ALT testing may identify injury without measuring clearance; direct drug concentrations or targeted pharmacokinetic assessments may be required when suspected interactions or altered clearance have clinical consequences.

Severity, Causality and Competing Diagnoses

When substantial enzyme abnormalities occur, chronology, biochemical pattern, symptom profile, bilirubin/INR, competing viral or biliary causes and all prescribed or nonprescribed exposures should be assessed. Severe DILI is an important but relatively uncommon clinical endpoint and referral or medication cessation decisions should follow the relevant drug-specific and hepatology guidance rather than an unsupported single threshold [1,2].

Polypharmacy and Inflammation

Multiple agents may share enzymes or transporters, while systemic inflammation may modify enzyme expression independently of medication changes. These mechanisms can amplify variability in clinical drug exposure. Individual interactions must be assessed with reference to known substrates and the patient's actual regimen, rather than assuming that all concomitant prescribing causes hepatotoxicity [4–6,9,11].

Monitoring Implications

Monitoring should be determined by drug class, known safety signals, comorbidity and clinical presentation. Baseline liver tests may be valuable for hepatotoxic regimens and high-risk patients; repeat testing should be individualized. Newly abnormal results require assessment of timing, repeatability, symptoms, bilirubin and alternative diagnoses. Enzyme induction alone should not be termed hepatocellular injury (Table 9).

Limitations and Research Implications

A broad comparison of chronic pharmacotherapy spans clinically dissimilar therapeutic classes; findings from selected adjudicated DILI populations cannot yield incidence among all long-term drug users. Some supporting numbers derive from previously completed reviews, not from original studies newly selected here. Future research should use treatment-defined longitudinal cohorts, prespecified DILI criteria, exposure ascertainment, baseline disease control, medication levels when relevant and transparent follow-up.

CONCLUSION

Long-term pharmacotherapy may produce hepatic biochemical changes, alter drug-metabolizing activity and affect physiological functions, but these outcomes are not interchangeable. Published findings reveal substantial variation by medication class, baseline disease and clinical context. Safe long-term prescribing requires exposure-aware interpretation of liver tests, assessment of relevant interactions and individualized follow-up. More comparable longitudinal primary evidence is necessary to estimate class-specific risks and establish the value of tailored monitoring strategies.

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