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Clinical Use, Biochemical Response, and Toxicity of Mitotane in Endogenous Cushing Syndrome: A Systematic Review and Evidence Map

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Systematic Review

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Abstract

Purpose:

Mitotane is an adrenolytic and steroidogenesis-modifying drug with an established role in adrenocortical carcinoma (ACC), but it has also been used in patients with difficult-to-control endogenous Cushing syndrome (CS). Its role outside ACC remains uncertain because the available literature includes historical series, referral-center cohorts, combination rescue regimens, pediatric cases, and case reports with differing treatment goals. This systematic review aimed to define the clinical settings in which mitotane has been used for endogenous CS and to summarize biochemical response, time to control, durability of response, treatment exposure, and toxicity, while distinguishing mitotane-dominant therapy from concurrently initiated combination regimens and oncologic treatment of functioning ACC.

Methods:

PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library were searched from inception through 28 June 2026 using the supplied review dataset. Backward and forward citation searching, reference checking of major reviews, and an eligibility re-audit were updated on 7 August 2026. Reports of patients with biochemically confirmed endogenous CS treated therapeutically with oral mitotane were eligible. Cushing disease (CD), ectopic ACTH syndrome (EAS), other ACTH-dependent or adrenal causes of CS, and cortisol-secreting ACC were considered separately. Non-functioning ACC was excluded from CS-specific efficacy analyses. Complete biochemical control was defined preferentially by normalization of urinary free cortisol (UFC) or by the accepted biochemical criterion used in the individual study. Because of substantial clinical and methodological heterogeneity, study-level findings were emphasized and no overall pooled estimate of efficacy, mortality, or toxicity was calculated.

Results:

Twenty primary reports were included. Among the largest mitotane-dominant datasets, Luton et al. reported remission in 38 of 46 patients with CD treated with mitotane alone, while Donadille et al. reported UFC normalization in 21 of 23 patients with EAS. In the series by Baudry et al., 48 of 67 long-term treated patients with CD achieved remission, with a median time to remission of 6.7 months. Smaller historical series also reported high response proportions. Schteingart et al. described remission in 29 of 36 patients receiving low-dose mitotane together with pituitary irradiation. In contrast, Kamenicky et al. demonstrated rapid biochemical control in severe ACTH-dependent CS when mitotane, metyrapone, and ketoconazole were initiated simultaneously, making it impossible to attribute the early response specifically to mitotane. A 2024 EAS case series also described sustained cortisol control in three patients with advanced pancreatic neuroendocrine tumors. Reported adverse effects included gastrointestinal, neurological, hepatic, lipid, thyroid, gonadal, and adrenal or mineralocorticoid disturbances. Overall certainty of evidence was very low because the available studies were non-

randomized, frequently included co-interventions, used heterogeneous outcome definitions, and were subject to substantial selection bias.

Conclusion:

Mitotane can achieve substantial and sometimes durable control of hypercortisolism in selected patients with endogenous CS, particularly when prolonged adrenal-directed therapy is required and in patients with functioning ACC. Its relatively slow onset limits its use as sole therapy in acute, life-threatening hypercortisolism. The available evidence supports individualized use in specialist practice rather than reliance on a single pooled estimate of efficacy. Prospective multicenter studies with standardized biochemical endpoints, time-to-control measures, therapeutic drug monitoring, and systematic adverse-event reporting are needed.

INTRODUCTION

Endogenous Cushing syndrome is uncommon but clinically important because sustained cortisol excess causes major cardiovascular, metabolic, infectious, thromboembolic, skeletal, muscular, and neuropsychiatric morbidity and contributes to excess mortality[1, 2]. Definitive treatment is directed toward the source of cortisol excess whenever feasible. Medical therapy is required when surgery is delayed, contraindicated, unsuccessful, or unlikely to provide sufficiently rapid control, and it may be used before surgery, after recurrence, or while awaiting the effect of radiotherapy [1–5].

Mitotane (o,p'-DDD) differs from conventional reversible steroidogenesis inhibitors. In addition to inhibiting adrenal steroidogenesis, it has adrenolytic effects, accumulates in adipose tissue, has a prolonged and highly variable elimination phase, induces CYP3A4, and increases cortisol-binding globulin. These properties can produce sustained cortisol suppression but also complicate dose titration, biochemical monitoring, glucocorticoid replacement, and drug-interaction management [6–9].

Historically, mitotane was used extensively in CD before contemporary pituitary surgery and newer medical therapies became widely available. Important series include Temple et al., Orth and Liddle, Luton et al., Schteingart et al., and later Baudry et al. [10–14]. In EAS, Donadille et al. reported long-term adrenal-directed treatment, while Kamenicky et al. used mitotane as one component of simultaneous triple-drug rescue therapy [15, 16]. More recent reports describe low-dose use in children, very long-term treatment, EAS due to pancreatic or thymic neuroendocrine tumors, and endocrine control in functioning ACC[17–21].

Previous systematic reviews of medical treatment for CS have reported drug-level pooled response estimates, but the mitotane literature is especially vulnerable to misleading aggregation because treatment intent, co-interventions, eras of practice, assays, and follow-up differ substantially[22]. The rationale for the present review is therefore not to generate a single efficacy percentage. Instead, we sought to reconstruct and critically map the available clinical evidence, distinguish independent or

mitotane-dominant effects from combination treatment, describe time to control and durability, and place toxicity and monitoring in a contemporary clinical context.

METHODS

Design and reporting

This systematic review and evidence map was structured according to PRISMA 2020 and PRISMA-S reporting principles [23, 24]. The review protocol was registered with PROSPERO (CRD420261476030). Owing to marked clinical heterogeneity, no overall pooled efficacy or safety estimate was used as the primary synthesis.

Eligibility criteria

Eligible reports described patients with biochemically confirmed endogenous CS who received oral mitotane with therapeutic intent and reported clinically interpretable efficacy or safety information. Eligible etiologies were CD, EAS, other ACTH-dependent or non-malignant adrenal CS, and cortisol-secreting ACC. Non-functioning ACC without documented endogenous hypercortisolism was excluded from CS-specific efficacy counts. Prospective or retrospective cohorts, uncontrolled series, and case reports were eligible because of the rarity and historical nature of the evidence base. Reviews, editorials, non-human studies, duplicate reports, conference abstracts without adequate clinical data, mechanistic studies without therapeutic intent, and reports without relevant efficacy or safety outcomes were excluded.

Treatment context was classified as: (1) mitotane monotherapy or mitotane-dominant treatment; (2) mitotane with previous or background therapy; (3) concurrently initiated combination therapy in which another cortisol-lowering drug was started at the same time; or (4) oncologic mitotane in functioning ACC. The third category was not interpreted as an estimate of the independent efficacy of mitotane.

Information sources and search strategy

The supplied electronic search covered PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library from inception through 28 June 2026. Search terms combined controlled vocabulary and free-text variants for mitotane (mitotane, Lysodren, o,p'-DDD, o,p DDD) with Cushing syndrome, Cushing disease, ectopic ACTH syndrome, and hypercortisolism. The supplied search retrieved 4,821 records: PubMed/MEDLINE 418, Embase 2,518, Scopus 1,758, and the Cochrane Library 127. The complete syntax is reproduced in **Supplementary Table S1**.

Because the initial included set was incomplete, backward and forward citation searching was repeated using the included articles, major Cushing disease reviews, and contemporary reviews of medical therapy. Eligibility was re-audited through 7 August 2026. This process identified 11 eligible primary

reports not represented in the original nine-report set, including the historical Temple, Orth, Luton, Schteingart, and Koide reports and a recent EAS case series by Hu et al. The resulting evidence map comprised 20 primary reports (Fig. 1**).**

Study selection, extraction, and outcomes

The source dataset reported removal of 985 duplicates, screening of 3,836 records, exclusion of 3,474 records at title/abstract level, 362 reports sought for retrieval, four reports not retrieved, 358 full texts assessed, and 349 full-text exclusions. The source files did not preserve article-level reason counts for these 349 exclusions; therefore, no numerical reason-specific breakdown was reconstructed.

Extracted variables included etiology, study design, age group, sample size, baseline biochemical severity when available, prior treatment, mitotane dose and duration, concomitant cortisol-lowering treatment, glucocorticoid replacement, plasma mitotane concentration, response definition, time to response, durability, recurrence after withdrawal, adverse effects, and treatment discontinuation.

The primary efficacy outcome was complete biochemical control, defined preferentially as normalization of 24-hour UFC or the study-specific accepted biochemical criterion. Partial biochemical responses and clinical endpoints were reported separately. Safety outcomes included gastrointestinal and neurological toxicity, hepatic dysfunction, dyslipidemia, thyroid and gonadal effects, mineralocorticoid deficiency, adrenal insufficiency, dose modification, and discontinuation. Mortality was described by clinical context and was not pooled as a drug-safety endpoint.

Methodological appraisal and certainty

Because most evidence was non-randomized and several reports were historical case series, methodological appraisal was domain based rather than presented as a formal numerical risk-of-bias score. Cohort-level interpretation was informed by ROBINS-I domains, while uncontrolled series and case reports were assessed using domains consistent with JBI critical appraisal tools [25]. Certainty was summarized using a GRADE-informed approach considering risk of bias, inconsistency, indirectness, imprecision, and selective publication [26].

Statistical presentation

For studies with a clear event denominator, study-level proportions are shown with Wilson 95% confidence intervals. No overall pooled estimate was calculated because the key assumptions required for clinically meaningful pooling were not met. In particular, older CD cohorts with or without radiotherapy, EAS cohorts, pediatric CD, simultaneous triple therapy, and functioning ACC address different questions. A low statistical heterogeneity estimate from a small number of such studies would not establish clinical homogeneity [27].

RESULTS

Study selection and scope of evidence

The final evidence map contained 20 primary reports spanning 1966 to 2026. The evidence included historical CD treatment series, an EAS referral-center cohort, a severe ACTH-dependent rescue cohort, pediatric CD, mechanistic and drug-interaction reports with therapeutic relevance, long-term case reports, a neurological safety series, EAS due to pancreatic and thymic neuroendocrine tumors, and functioning ACC. The distribution of evidence across clinical settings is shown in Fig. 2. Because some referral-center reports were produced in overlapping eras and because mixed-etiology publications sometimes included more than one CS subtype, patient numbers were not simply added to generate a unique-person denominator across the whole literature. The characteristics and treatment context of all included primary reports are summarized in Table 1.

Table 1
Included primary reports and treatment context

Report	N	Population	Mitotane context	Main contribution
Southren 1966 [28]	2 therapeutic cases	Mixed: non-tumorous adrenal hyperfunction and functioning ACC	1–10 g/day	Clinical/biochemical improvement; high-dose GI toxicity
Temple 1969 [10]	4	CD	~ 3 g/day	Cortisol secretion reduced after several months without aldosterone deficiency
Hellman 1970 [29]	1	CS	3 g/day for 60 days	Flattening/reduction of cortisol secretory pattern
Orth 1971 [11]	8 mitotane-treated	CD within 108-patient CS series	3–6 g/day in later synthesis	Serum cortisol normalized without mineralocorticoid deficiency
Wortsman 1977 [30]	1	Pituitary-dependent CS	Mitotane with then without spironolactone	Response became apparent after spironolactone withdrawal
Luton 1979 [12]	62: 46 mitotane alone; 16 + pituitary RT	CD	4–12 g/day	38/46 remission with mitotane alone; 16/16 with RT
Schteingart 1980 [13]	36	CD	1.5-2 g/day + pituitary RT	29/36 clinical and biochemical remission
Koide 1985 [14]	3	EAS, CD, adrenal cancer	o,p'-DDD	Demonstrated discordance of urinary 17-OHCS during therapy; UFC/plasma cortisol preferred
Otokida 1986 [31]	1	Functioning ACC	Low-dose	Tumor regression and lower urinary 17-OHCS; plasma cortisol remained high
du Rostu 1987 [32]	12 total; 7 CS	CS and ACC	Long-term exposure	Neurological toxicity series; all had mild symptoms, half major complications
Knappe 1997 [33]	6	Hypothalamic-pituitary CS	~ 3 g/day initially	UFC normalized between months 2 and 10
Kawai 1999 [34]	1	Intractable CD	Long-term	18-year treatment experience

Report	N	Population	Mitotane context	Main contribution
Donadille 2010 [15]	23	EAS	Mean 3.3 ± 1.2 g/day; transient co-treatment in some	UFC normalized in 21/23; long follow-up
Kamenicky 2011 [16]	11	Severe ACTH-dependent CS	Mitotane + metyrapone + ketoconazole started together	Rapid rescue; early effect not attributable to mitotane alone
Baudry 2012 [35]	76 treated; 67 long-term efficacy	CD	Mean ~ 2.5 g/day	48/67 remission; median 6.7 months
Motte 2018 [17]	9	Pediatric CD	Low-dose monotherapy, up to 2 g/day	Growth/BMI/puberty improved; cortisol control delayed/inconsistent
Seibold 2024 [18]	1	CD	Very long-term	37 years of treatment, including two pregnancies before current risk knowledge
Hu 2024 [19]	3	EAS from advanced pancreatic NET	Low-dose maintenance after initial therapy	All three achieved rapid and sustained cortisol control; mild appetite loss/dizziness
Tucci 2025 [20]	4 ACC; 2 with overt cortisol-secreting CS	Functioning ACC subgroup	Long-term oncologic mitotane + local therapies	Useful for toxicity/long-term context; only 2/4 are CS cases
Zhou 2026 [21]	1	EAS from thymic carcinoid	Preoperative 1–2 g/day	~ 85% UFC reduction within 13 days; exceptional rapid case

Biochemical response and time to control

The most interpretable mitotane-dominant studies show that biochemical response can be substantial but is not uniform, and in typical use develops over weeks to months. Temple et al. reported successful reduction of cortisol secretion in all four patients after several months of low-dose treatment [10]. Orth and Liddle reported normalization of serum cortisol in eight mitotane-treated patients with CD [11]. Luton et al. obtained remission in 38 of 46 patients treated with mitotane alone after an initial treatment period averaging about eight months; the 16 patients also receiving pituitary irradiation all entered remission, but this combined group cannot be used to estimate mitotane-only efficacy [12].

Donadille et al. reported UFC normalization in 21 of 23 patients with EAS, with urinary cortisol falling from 2,603 ± 3,443 micrograms/day before treatment to 79 ± 169 micrograms/day at maximal efficacy [15]. Baudry et al. reported remission in 48 of 67 long-term treated patients with CD (71.6%), with a median 6.7 months to remission and a mean plasma mitotane concentration of 10.5 ± 8.9 mg/L at

remission [35]. Knappe et al. reported UFC normalization in all six patients between months 2 and 10 [33]. The principal biochemical outcomes, time to response, and attribution of treatment effect are summarized in Table 2, while study-level remission estimates with available denominators are shown in Fig. 3 without a pooled summary.

Schteingart et al. reported clinical and biochemical remission in 29 of 36 patients given low-dose mitotane concurrently with or after pituitary cobalt irradiation [13]. Although the authors considered the initial remission mainly adrenal in origin, the co-intervention and historical treatment setting mean this study should be interpreted separately from mitotane-alone cohorts.

The Kamenicky cohort addressed acute rescue rather than isolated mitotane efficacy. Median UFC fell from 2,737 micrograms/24 h to 50 micrograms/24 h within 24–48 hours after mitotane, metyrapone, and ketoconazole were initiated simultaneously [16]. This rapid response is pharmacologically more consistent with the faster-acting co-administered inhibitors. In seven patients, metyrapone and ketoconazole were later withdrawn after a median 3.5 months while control persisted on mitotane, supporting a role in sustained suppression after the acute phase.

The 2024 Hu series adds contemporary evidence in EAS from advanced pancreatic neuroendocrine tumors. All three patients had hypercortisolism controlled during mitotane-containing management and maintained long-term control on low-dose mitotane; in one described patient serum cortisol normalized after approximately seven days [19]. Because antitumor therapy was also being given, these cases support feasibility and durability but do not provide an uncontaminated estimate of mitotane monotherapy efficacy.

Table 2
Biochemical response, time to response, and attribution

Study	Outcome	Observed result	Time	Interpretation
Temple 1969 [10]	Reduction/correction of hypercortisolism	4/4	Several months	Very small historical CD series
Orth 1971 [11]	Serum cortisol normalized	8/8	Long-term follow-up	Mitotane subgroup within broader CS treatment series
Luton 1979 [12]	Clinical/biochemical remission	38/46 with mitotane alone	Mean initial treatment ~ 8 months	Largest historical mitotane-alone CD cohort
Donadille 2010 [15]	UFC normalization	21/23	Variable; long-term	EAS; some transient additional steroidogenesis inhibition
Baudry 2012 [35]	Normal 24-h UFC	48/67 (71.6%)	Median 6.7 months	Largest modern CD cohort
Knappe 1997 [33]	UFC normalization	6/6	2–10 months	Small uncontrolled pituitary CS series
Schteingart 1980 [13]	Clinical and biochemical remission	29/36 (80.6%)	Early and late responders	Pituitary irradiation co-intervention
Kamenicky 2011[16]	Rapid UFC control during rescue	11/11 improved	24–48 h	Simultaneous triple therapy; not mitotane-specific
Hu 2024 [19]	Serum cortisol control	3/3	Rapid in reported cases	Concurrent antitumor treatment; EAS
Motte 2018 [17]	Clinical growth/BMI/puberty; cortisol control	Clinical improvement; biochemical control inconsistent	~ 1 year for clinical endpoints	Pediatric outcomes not equivalent to adult UFC remission

Durability and recurrence after withdrawal

Mitotane-induced control during treatment should not be equated with cure of the underlying ACTH source. In the historical Luton cohort, relapse after initial remission was common, although repeated drug or radiotherapy courses could restore control [12]. In Baudry et al., recurrence was frequent after withdrawal among patients followed without immediate alternative treatment, with a median interval of approximately 13 months in those who relapsed [35]. These observations are consistent with persistent pituitary or ectopic disease despite prolonged adrenal suppression.

Long-term case reports demonstrate that sustained treatment can be feasible in highly selected patients. Kawai et al. reported 18 years of therapy for intractable CD [34], and Seibold et al. described 37

years of treatment with dose adjustments and extended clinical follow-up [18]. Such reports are valuable for feasibility and toxicity but are strongly affected by survivor and publication selection.

Pediatric disease and special settings

In nine children with CD, low-dose mitotane improved growth velocity, body mass index, and pubertal development after failed or incomplete definitive treatment, but biochemical control was delayed and inconsistent [17]. These outcomes are clinically important and should not be collapsed into adult UFC-normalization estimates. Long-term endocrine toxicity and reproductive implications require particular attention in younger patients.

A notable recent case by Zhou et al. described an adolescent with an ACTH-secreting thymic carcinoid and extreme hypercortisolism in whom preoperative mitotane monotherapy was followed by an approximately 85% reduction in UFC within 13 days [21]. This unusually rapid response is clinically interesting but should not be used to redefine the usual onset of action on the basis of a single exceptional case.

Functioning adrenocortical carcinoma

Functioning ACC was deliberately separated because mitotane has simultaneous oncologic and endocrine objectives and because tumor-directed therapies strongly influence outcome. Historical reports document cortisol-lowering effects but also show that urinary steroid metabolites can become unreliable during mitotane therapy [14, 31]. In the Tucci case series, only two of four long-term metastatic ACC survivors had overt cortisol-secreting CS; the two non-functioning tumors were excluded from CS-specific interpretation [20]. Contemporary ACC guidance continues to position mitotane as a central systemic therapy, with more rapid steroidogenesis inhibition required when cortisol excess is severe [6].

Safety, endocrine effects, and monitoring

Gastrointestinal intolerance is the most consistent dose-limiting adverse effect, particularly at higher historical doses, and includes anorexia, nausea, vomiting, abdominal discomfort, and diarrhea [10, 12, 13, 28]. Neurological toxicity ranges from subtle fatigue or concentration difficulty to dizziness, ataxia, confusion, memory impairment, and more severe central or peripheral manifestations. The du Rostu safety series is notable because all 12 exposed patients had mild neurological symptoms and half experienced major complications; seven of these patients had CS [32].

Hepatic enzyme abnormalities and dyslipidemia are also well recognized. Thyroid dysfunction can show a central pattern with low free T4, while hypogonadism, gynecomastia, and reproductive effects can occur during prolonged therapy [8, 9]. Adrenal insufficiency may be an intended pharmacodynamic consequence of effective adrenal suppression but can become symptomatic or persistent. Mineralocorticoid deficiency is less predictable in non-ACC low-dose use but must be considered when hypotension, hyperkalemia, or salt craving develops.

Mitotane is a strong CYP3A4 inducer and increases cortisol-binding globulin. Consequently, total serum cortisol may be difficult to interpret and hydrocortisone requirements can be substantially higher than in ordinary adrenal replacement [2, 8]. Monitoring should therefore integrate clinical assessment with UFC and/or salivary cortisol for hypercortisolism, electrolyte status, liver enzymes, lipids, free T4, gonadal function when relevant, neurological and gastrointestinal symptoms, medication interactions, and plasma mitotane concentrations when available. Pregnancy should be avoided because of teratogenicity and prolonged persistence of the drug after withdrawal [2–5]. The principal safety signals and corresponding monitoring implications are summarized in Table 3.

Table 3
Main safety signals and monitoring implications

Domain	Reported manifestations	Clinical implication
Adrenal	Biochemical/symptomatic adrenal insufficiency; occasionally persistent suppression	Plan glucocorticoid replacement when needed; assess symptoms, blood pressure, sodium and potassium
Gastrointestinal	Anorexia, nausea, vomiting, abdominal discomfort, diarrhea	Common dose-limiting toxicity; review adherence, nutrition, dose escalation
Neurological	Fatigue, concentration/memory problems, dizziness, ataxia, confusion	Clinical review at each visit; check exposure and reduce/interrupt dose when indicated
Hepatic	Transaminase or gamma-GT elevation; hepatitis reported	Periodic liver chemistry
Lipid	Hypercholesterolemia and broader dyslipidemia	Periodic lipid profile and cardiovascular risk treatment
Thyroid	Low free T4/central-pattern dysfunction	Monitor free T4; TSH alone may be misleading
Gonadal/reproductive	Hypogonadism, gynecomastia, reproductive effects; teratogenicity	Assess clinically; avoid pregnancy; individualized reproductive counseling
Drug interactions	Strong CYP3A4 induction; altered glucocorticoid metabolism	Medication reconciliation; higher glucocorticoid replacement may be required
Therapeutic exposure	Long and variable half-life; delayed accumulation	Plasma mitotane monitoring where available; dose changes have delayed effects

Methodological appraisal and certainty of evidence

The evidence base is limited not only by small sample size but by several forms of bias. Historical cohorts were often treated before current diagnostic assays and surgery standards; referral-center cohorts select complex disease; radiotherapy and other steroidogenesis inhibitors were common co-

interventions; response definitions varied; and adverse events were not collected with standardized denominators. Long-term case reports preferentially capture unusual survivors and successful treatment courses. These problems prevent precise causal estimation of a general 'mitotane response rate'. The domain-based methodological appraisal of the principal evidence sources is presented in Table 4.

On the basis of these limitations, certainty in the evidence for efficacy, rapid biochemical control, durability, and CS-specific toxicity was considered very low. The GRADE-informed certainty assessment for the major outcomes is summarized in Table 5.

Table 4
Domain-based methodological appraisal

Evidence	Main concerns	Overall concern for causal inference
Temple 1969 / Orth 1971 / Luton 1979	Historical CD cohorts; non-randomized; assay and treatment-era differences; some radiotherapy	Serious
Schteingart 1980	No untreated control; pituitary irradiation co-intervention	Critical for isolated mitotane efficacy
Donadille 2010	Retrospective single center; EAS selection; transient co-treatment in some	Serious
Kamenicky 2011	Selected life-threatening disease; three drugs started together	Critical for isolated mitotane efficacy; useful for regimen effectiveness
Baudry 2012	Retrospective single center; long-term efficacy subset; potential responder/follow-up selection	Serious
Motte 2018	Small pediatric retrospective cohort; biochemical control not the sole endpoint	Serious
Hu 2024	Three-patient case series; concurrent antitumor therapy	Critical for frequency estimation
Case reports / long-term series	No comparator; strong publication and survivor selection; variable assays	Critical for frequency estimation; useful for clinical context

Table 5
GRADE-informed certainty summary

Outcome	Evidence base	Certainty	Reason
Complete biochemical control with mitotane-dominant therapy	Historical and modern uncontrolled cohorts	Very low	Non-randomized design, inconsistency in definitions and eras, imprecision, selection
Rapid control in severe ACTH-dependent CS	One 11-patient simultaneous triple-therapy cohort plus cases	Very low	Cannot isolate mitotane effect; extreme disease; co-intervention
Durability / recurrence after withdrawal	Mainly Luton, Baudry, and selected long-term reports	Very low	Responder selection, variable follow-up, sparse standardized recurrence data
Gastrointestinal / neurological toxicity	Cohorts, safety series, case reports; supported by ACC literature	Very low for CS-specific incidence	Selective ascertainment, inconsistent denominators, indirectness
Mortality	Heterogeneous etiologies and follow-up	Not interpretable as drug effect	Dominated by malignancy, disease severity, and competing risks

DISCUSSION

This updated review materially changes the interpretation of the earlier draft. The central message is no longer that a small meta-analysis suggests approximately 94% biochemical control. That estimate was derived from clinically incompatible treatment settings and omitted several important historical cohorts. After the eligibility audit, the evidence is broader and more internally coherent: mitotane has repeatedly produced substantial cortisol suppression, but the size and speed of its independent effect vary according to disease etiology, dose, co-intervention, and treatment era.

The strongest evidence for mitotane as the main adrenal-directed agent comes from CD and EAS. In CD, remission proportions in the larger historical and modern cohorts were approximately 72–83%, while smaller series often reported higher rates [11, 12, 35]. In EAS, Donadille et al. reported UFC normalization in 21/23 patients [15]. These results agree with contemporary reviews and guidelines that regard mitotane as an effective but relatively slow adrenal-directed therapy and explain why it is now used less frequently than faster and more easily titrated steroidogenesis inhibitors in many centers [2–5].

Time to control is clinically decisive. The typical course in CD is measured in months, not hours. The median time to remission in Baudry et al. was 6.7 months [35], and historical reports also describe a gradual effect. Therefore, severe acute hypercortisolism should not be managed with mitotane alone. The Kamenicky experience is best understood as a sequential pharmacologic strategy: faster agents provide immediate blockade, while mitotane accumulates and can later support sustained suppression

[16]. The 2026 thymic carcinoid case demonstrates that rapid responses can occur, but a single exceptional case should not override the broader pharmacologic pattern [21].

The evidence also clarifies why outcome measurement matters. Mitotane changes steroid metabolism and raises cortisol-binding globulin. Older urinary 17-hydroxycorticosteroid measurements can fall without parallel changes in plasma cortisol or UFC, as shown by Koide et al. and Otokida et al. [14, 31]. Contemporary monitoring should therefore rely on validated cortisol measures and clinical status rather than legacy steroid metabolites. This is particularly important when interpreting older studies or comparing historical and modern response rates.

Functioning ACC should remain a separate stratum. In that setting, mitotane is being prescribed not merely as a cortisol-lowering drug but as systemic oncologic therapy, and target exposure, treatment duration, prognosis, and co-interventions differ fundamentally from non-malignant CS[6]. Severe cortisol excess in ACC often requires a faster cortisol-lowering drug in addition to mitotane, whereas milder secretion may be controlled as mitotane accumulates. Mixing functioning ACC with CD or EAS in a single efficacy proportion would therefore be clinically misleading.

The main limitation of mitotane is not lack of cortisol-lowering activity but the balance between delayed accumulation, prolonged persistence, drug interactions, and multi-system toxicity. Gastrointestinal symptoms may prevent dose escalation, neurological effects can be subtle until exposure is substantial, dyslipidemia and liver abnormalities require surveillance, and thyroid, gonadal, and adrenal replacement issues create a considerable monitoring burden [8, 9, 32]. These characteristics favor use in centers familiar with therapeutic drug monitoring and adrenal replacement.

The literature also illustrates a change in practice over time. In the 1960s to 1980s, mitotane was a major nonsurgical treatment for CD and was sometimes combined with pituitary irradiation. Today, transsphenoidal surgery remains first line for operable CD, and newer adrenal steroidogenesis inhibitors provide faster and more titratable options [1–5]. Mitotane therefore occupies a narrower but still meaningful niche: durable adrenal-directed suppression in selected refractory or persistent disease, selected EAS, bridging after acute control, and functioning ACC.

This review has limitations. The underlying search dataset did not preserve article-level reasons for 349 full-text exclusions, and the later eligibility audit identified reports missed from the original included set. We have made this transparent rather than reconstructing unsupported counts. The evidence itself is mostly observational, many studies are historical, and overlap between referral-center populations cannot always be fully excluded. Outcome definitions, doses, assays, and follow-up differ, and case reports strongly favor unusual successful or long-duration experiences. These limitations are precisely why the present manuscript emphasizes an evidence map and study-level interpretation rather than a pooled efficacy estimate.

Despite these limitations, the expanded evidence base provides a clearer clinical rationale. Mitotane is a potent but slow and management-intensive adrenal-directed treatment. It should be selected according

to the time horizon of cortisol control, underlying etiology, availability of definitive therapy, comorbidities, reproductive plans, drug interactions, and local expertise. Figure 4 summarizes this practical positioning.

CONCLUSION

Mitotane can produce substantial and sometimes durable cortisol suppression in selected patients with endogenous Cushing syndrome. The best-supported non-ACC use is as a specialist adrenal-directed option when sustained suppression is required, particularly in persistent or recurrent CD and selected EAS. In functioning ACC it has a distinct combined oncologic and endocrine role. Its usual delayed onset makes it unsuitable as the sole initial treatment of life-threatening hypercortisolism, where faster-acting therapy is required. The current literature does not justify a single pooled mitotane efficacy or mortality estimate. Future multicenter studies should use standardized biochemical definitions, report time to control and durability, document co-interventions and plasma exposure, and collect adverse events using predefined denominators and severity grades.

DATA AVAILABILITY

All data used in this review were derived from published reports and are summarized in the manuscript and supplementary material. No individual participant dataset was generated.

Declarations

Competing Interests

The authors declare that they have no competing financial or non-financial interests related to this work.

Ethics Approval

Ethics approval was not required because this study was a systematic review of previously published data and did not involve direct participation of human subjects or access to identifiable individual-level data.

Consent to Participate

Not applicable.

Consent for Publication

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Author Contribution

V.J. contributed to conceptualization, literature search, data curation, formal analysis, interpretation of data, and preparation of the original manuscript draft. M.V. contributed to literature screening, data extraction, formal analysis, and interpretation of data. D.B. contributed to methodology, supervision, interpretation of data, and critical review and editing of the manuscript. P.D. and R.W. contributed to interpretation of the clinical findings and critical review and editing of the manuscript. S.K.B. contributed to conceptualization, supervision, interpretation of data, critical revision of the manuscript, and final approval of the work. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data Availability

All data analysed in this systematic review were obtained from published studies included in the review. Data extracted and generated during the review are available from the corresponding author on reasonable request.

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Figures

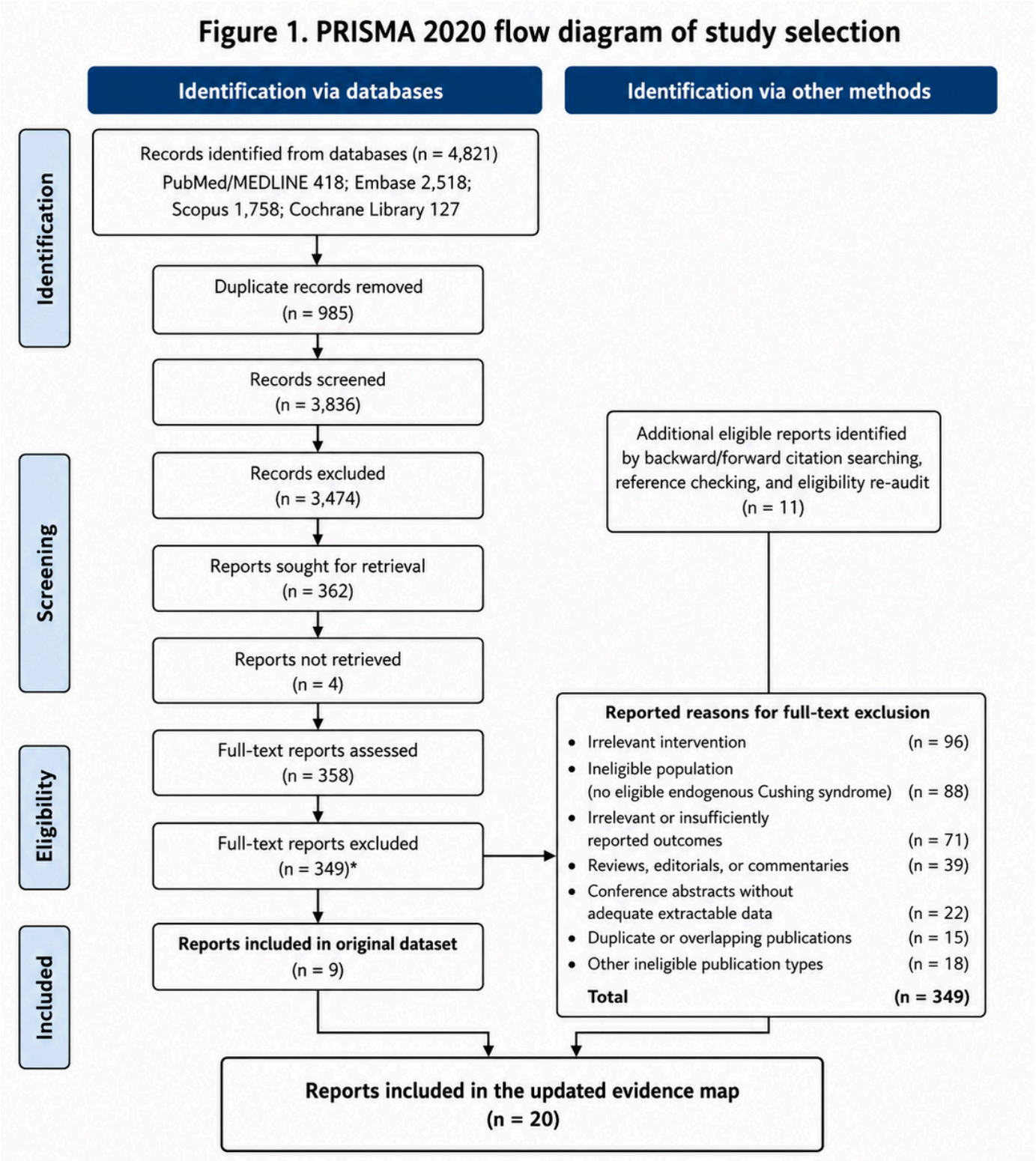


Figure 1

Prisma Flow Diagram of Study Selection.

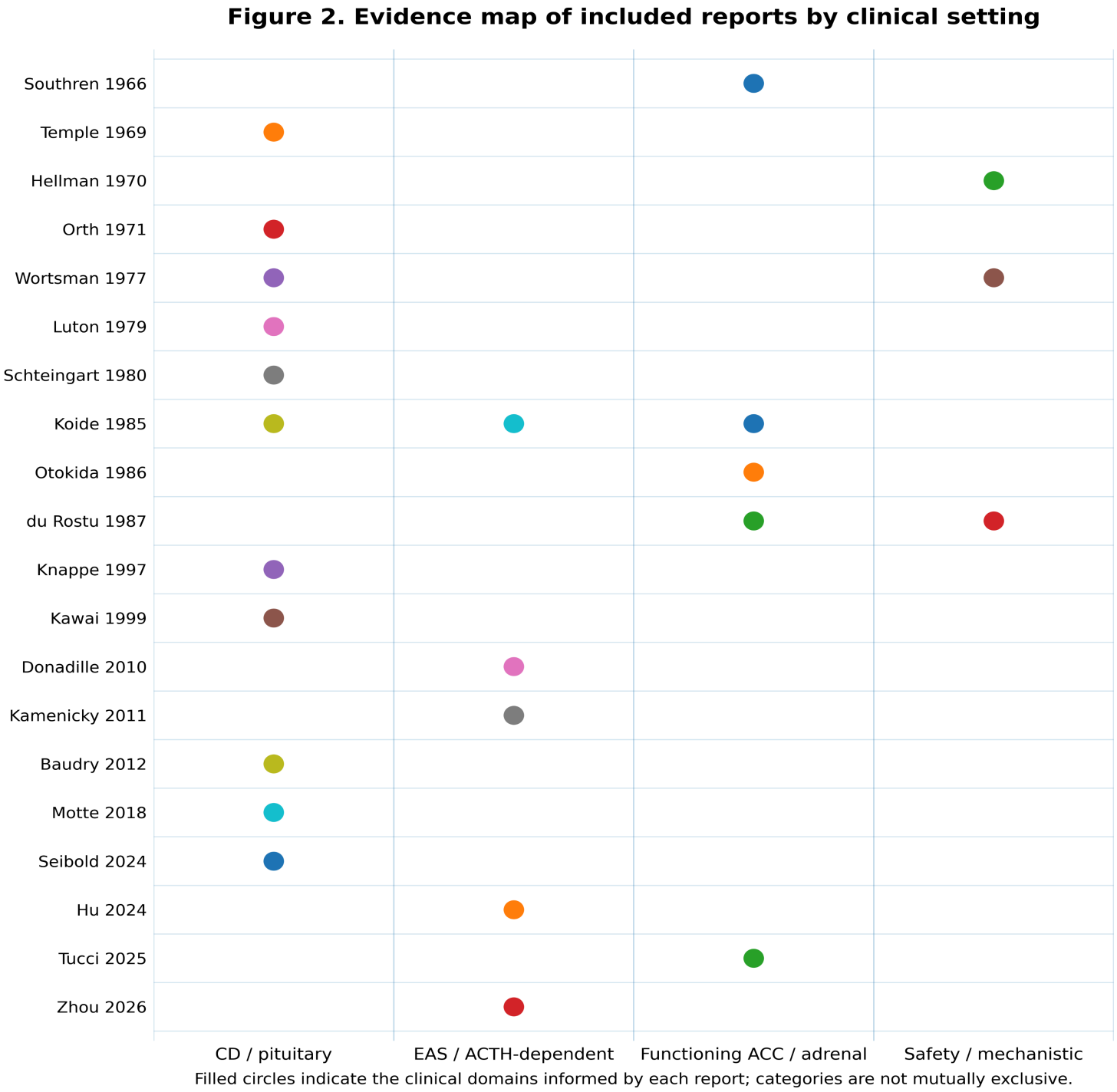
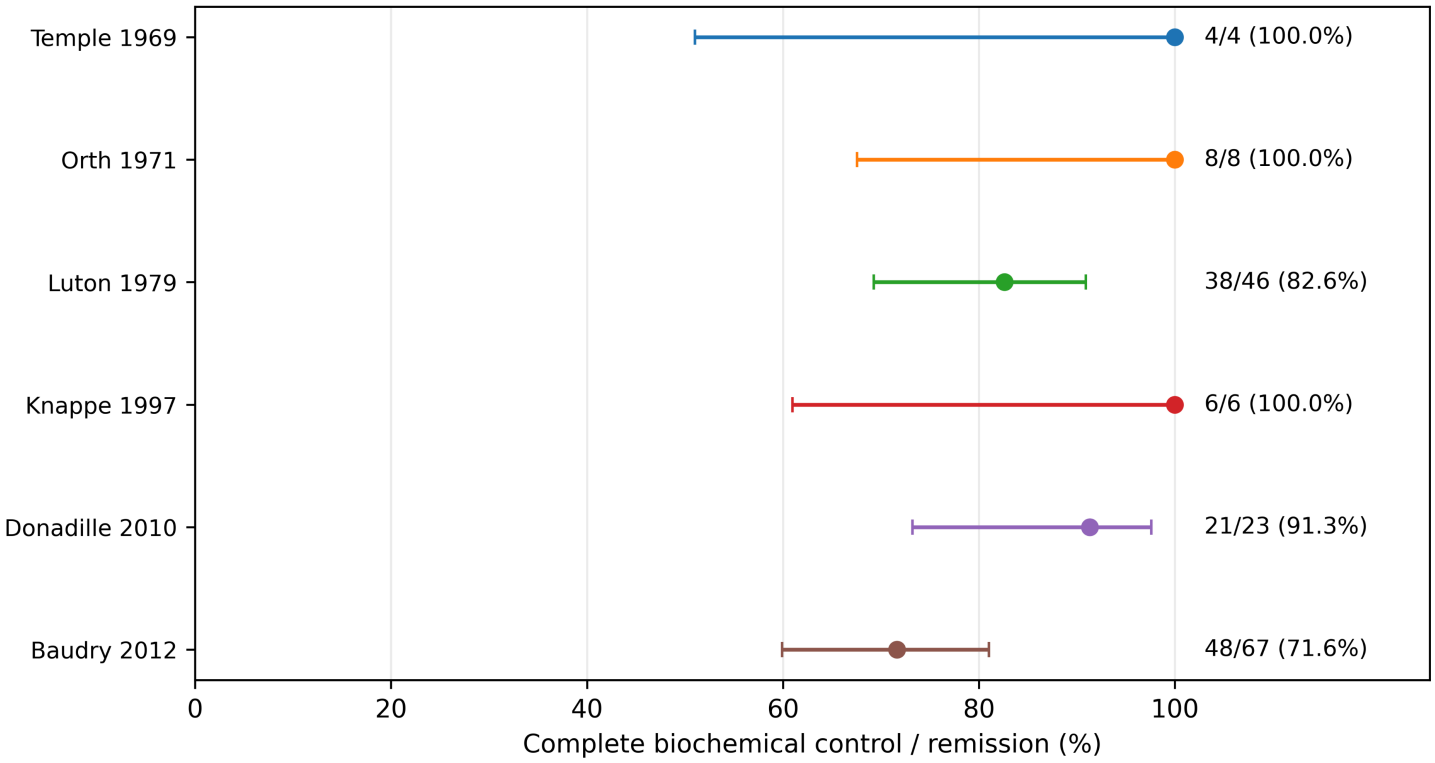


Figure 2

Evidence map of included reports by clinical setting. A report can contribute to more than one domain. CD, Cushing disease; EAS, ectopic ACTH syndrome; ACC, adrenocortical carcinoma.

Figure 3. Study-level biochemical control with mitotane-dominant therapy



Wilson 95% confidence intervals. No pooled estimate is shown because definitions, eras, populations, co-interventions, and follow-up were clinically heterogeneous.

Figure 3

Study-level complete biochemical control or remission in reports where mitotane was the principal cortisol-lowering treatment and a clear denominator was available. Wilson 95% confidence intervals are shown. No pooled estimate is presented because definitions, treatment eras, co-interventions, and populations are clinically heterogeneous.

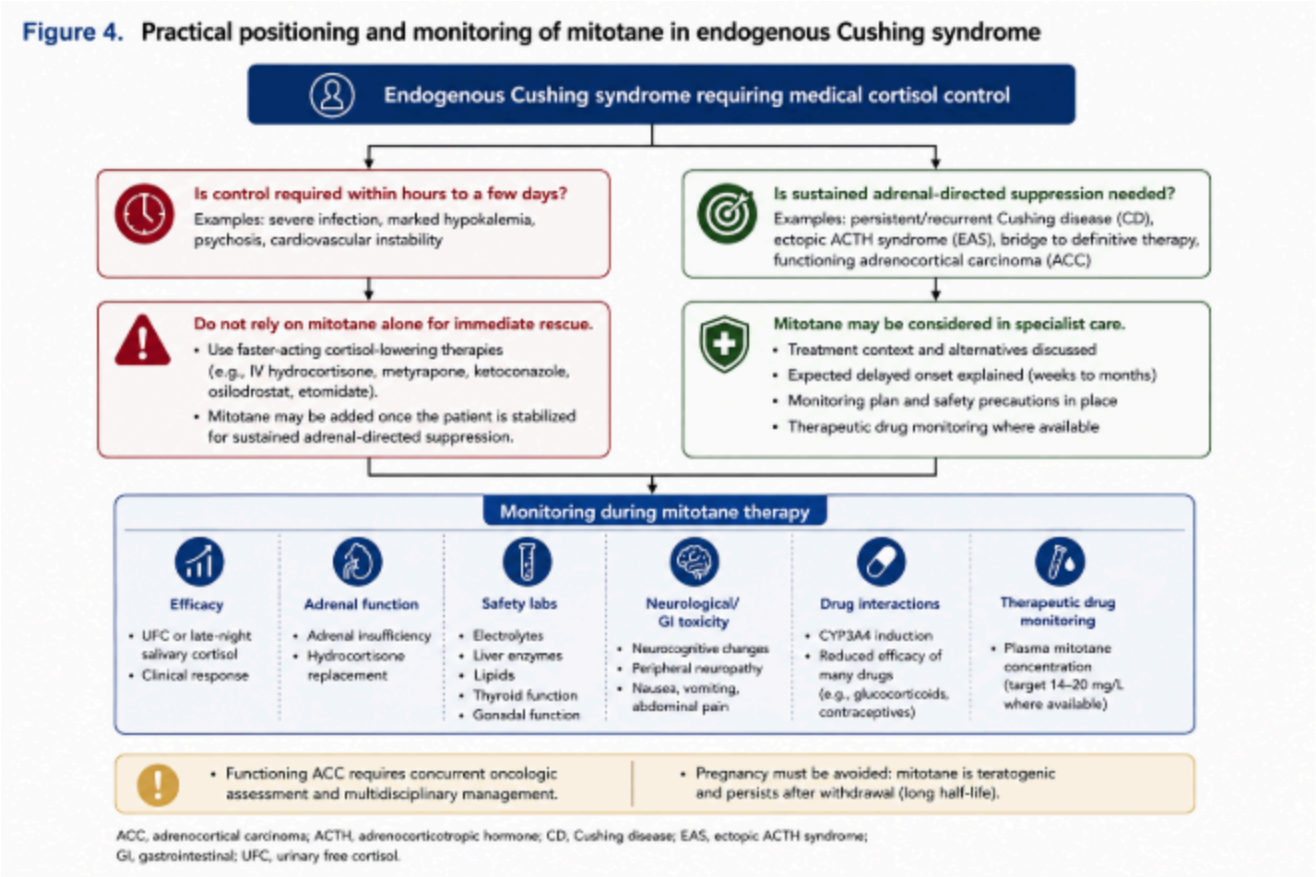


Figure 4

Practical positioning and monitoring of mitotane in endogenous Cushing syndrome. This evidence-based schematic summarizes the treatment contexts identified in the review and should be applied alongside disease-specific guidelines and specialist clinical judgment.

Supplementary Files

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