Hormonaly ACADEMY

QUANTITATIVE & INTERACTIVE EDITION (v2) · FOR LICENSED CLINICIANS

GLP-1 and Incretin Therapies

How they work, how to use them, and the law

An evidence-graded clinical reference with 18 native vector plates and 3 study-level quantitative syntheses — covering receptor pharmacology, cardiorenal HKSJ/prediction-interval forest plots, cross-program T2D vs non-T2D effect ratios, DXA lean-mass preservation, annualized event-rate scaling vs NAION & E-values, 4 source-badged bedside algorithms, pipeline, and global pricing.

Interactive v2 · 18 Plates & Meta-Analyses

Open 18-Plate Directory →

GLP-1 · 7-36 amide

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Fady Hannah-Shmouni, MD FRCPC

Endocrinologist and biochemical geneticist

EVIDENCE MONOGRAPH · QUANTITATIVE & INTERACTIVE CLINICAL EDITION (v2)

GLP-1 and Incretin Therapies

How they work, how to use them, and the law

An interactive, evidence-graded reference for licensed clinicians, with regulatory and clinical-trial verification through 11 November 2026. Includes 18 vector visual plates and 3 study-level quantitative syntheses — exploratory random-effects cardiorenal synthesis with Hartung–Knapp–Sidik–Jonkman and 95% prediction intervals (MA-1), exploratory cross-program ratio-of-treatment-effects synthesis across T2D vs non-T2D cohorts (MA-3), contextual annualized event-rate scaling vs FDA NAION with VanderWeele–Ding E-values (STAT-5), DXA lean-mass preservation, responder thresholds, pipeline, global pricing, and 4 source-badged clinical algorithms. Educational content for clinical reasoning — not medical advice for any individual, and not a protocol for any unapproved use.

Fady Hannah-Shmouni, MD FRCPC
Endocrinologist and biochemical geneticist

QUANTITATIVE & INTERACTIVE EDITION (v2) · VERIFIED THROUGH 11 NOVEMBER 2026

Hormonaly Academy · 2026

Contents

Visual, Meta-Analytic & Algorithm Directory (18 Vector Plates) 3
How to use this book 5
Incretin therapies at a glance 7
Algorithm 1 · Comorbidity & Phenotype-Guided Agent Selection 10

PART 01 · FOUNDATIONS 11

B 1 The incretin system: GLP-1, GIP and glucagon 12
Incretin and glucagon receptors at a glance 23
B 2 History and development of incretin therapies 24
Incretin therapies: agents, class and first approvals 30
A 3 Pharmacology of the approved agents 32
Formulations at a glance 44

PART 02 · CLINICAL USE 48

A 4 Obesity management 49
Weight loss by agent and dose in phase 3 obesity trials 69
5 Use beyond obesity: the widening set of indications 71
Indications beyond obesity at a glance 90
B 6 Dose-response across conditions 93
Dose-response by agent 105
C 7 Microdosing 107
Approved dosing: titration versus maintenance 114
B 8 Discontinuation, weight regain and long-term strategy 115
Continuation, withdrawal and post-cessation outcomes 128
B 9 Switching and sequential therapy 130
Algorithm 2 · Missed-Dose, Switching & Oral Maintenance Protocol 138
Switching scenarios and practical considerations 139
A 10 Adverse effects, monitoring and contraindications 141
Algorithm 3 · GI Escalation, Organ Red-Flags & Perioperative Airway 162
Monitoring schedule for GLP-1 and GIP/GLP-1 therapy 163

CONTENTS · CONTINUED

Semaglutide product matrix 167
11 The brain: reward, addiction and cognition 169
Brain and behavior: evidence at a glance 188
12 Cancer risk and cancer care 191
Cancer outcomes with incretin therapy: evidence 207

PART 03 · AGENTS AND PIPELINE 210

13 Retatrutide: the triple GIP/GLP-1/glucagon agonist 211
Retatrutide clinical evidence at a glance 221
14 The next-generation pipeline 224
Incretin and adjunct pipeline at a glance (2026) 243

PART 04 · LAW AND PRACTICE 246

15 Compounded, 'research use only' and gray-market GLP-1s 247
Algorithm 4 · Product Legality, 503A/503B & Gray-Market Verification 260
Compounding and shortage timeline, 2022 to 2026 261
16 Global access, pricing and generics 264
Semaglutide patent expiry and generic entry 281

APPENDIX A · SUPPLEMENTS AND ENDOGENOUS GLP-1 283

Supplements and endogenous GLP-1 at a glance 303
Supplements: main cautions 307

APPENDIX B · CLINICAL MATRIX AND TRIAL GLOSSARY 309

Comorbidity-to-agent clinical selection matrix 310
Master clinical trial acronym glossary 313

ABOUT 320

About the author 320
About this monograph 323

QUANTITATIVE & INTERACTIVE SUITE · 18 VECTOR PLATES & 3 QUANTITATIVE SYNTHESES

Visual & Interactive Plate Directory

Select any source-badged clinical algorithm, schematic, quantitative synthesis, or trial plate to jump directly.

CLICKABLE CLINICAL DECISION ALGORITHMS (4 · EPISTEMIC SOURCE-BADGED)

ALG 1 — Comorbidity & Phenotype-Guided Agent Selection — p. 10 →
MEN2/MTC formulation check · pancreatitis hold/individualized rule · SELECT, FLOW, OSA, MASH

ALG 2 — Missed-Dose Recovery, Switching & Oral Step-Down — p. 138 →
FDA missed-dose rules vs multi-miss extrapolation · within-sema vs cross-molecule · ATTAIN-MAINTAIN

ALG 3 — GI Escalation, Acute Organ Red-Flags & Perioperative Airway — p. 162 →
AKI guard · ACG/IAP 2-of-3 pancreatitis rule · 9 Nov 2026 FDA NAION · 2024 Multisociety POCUS/RSI

ALG 4 — Compounded, 'Research-Use-Only' & Gray-Market Verification — p. 260 →
NDA/BLA check · RUO/salt safe clinical transition · post-shortage 503A/503B & OFA v. FDA No. 25-10600

MECHANISTIC & PHARMACOKINETIC SCHEMATICS (2)

FIG 1.1 — Gut–Brain–Islet–Adipose–Liver Receptor Architecture — p. 22 →
Endogenous L/K/α-cell secretion, DPP-4 clearance & GLP-1R / GIPR / GCGR organ target map

FIG 3.1 — Elimination Half-Life & Structural Protraction Across Agents — p. 43 →
Logarithmic t½ span (1–2 min native GLP-1 to 21 d MariTide) · acylation, SNAC, small molecule & Fc

STUDY-LEVEL QUANTITATIVE SYNTHESES & CONFOUNDING SENSITIVITY PLATES (3)

FIG 5.1 — Cardiorenal Outcomes & MA-1 Random-Effects Synthesis — p. 76 →
FDA CV-labeled 3-pt MACE HR 0.85 (k=5, N=49,792; HKSJ 0.78–0.91; PI 0.78–0.92) & 2-study kidney HR 0.77

FIG 6.2 — Exposure Dissociation & MA-3 Exploratory RoTE Synthesis — p. 100 →
HbA1c plateau vs weight/dysesthesia slope + 7-pair T2D ÷ non-T2D RoTE 0.64 (N=20,160; ecological)

FIG 10.1 — Annualized Event-Rate Scaling vs NAION & STAT-5 E-Values — p. 156 →
FLOW/SELECT/SOUL rate diffs per 100k py vs +2.6 NAION excess (contextual) + confounding E-values

Continued on Next Page: 9 Trial Efficacy, Body-Composition, Pipeline & Pricing Plates →

VISUAL & INTERACTIVE PLATE DIRECTORY · CONTINUED

OBESITY, RESPONDER DISTRIBUTION, BODY COMPOSITION & WITHDRAWAL PLATES (6)

FIG 4.1 **Phase 3 Obesity Weight-Loss Dumbbell Comparison** p. 52 →
STEP 1, STEP UP (7.2 mg), OASIS 4, SURMOUNT-1, ATTAIN-1, SURMOUNT-5 & TRIUMPH-1 (-3.9% pbo)

FIG 4.2 **Categorical Weight-Loss Responder Thresholds & Heterogeneity** p. 55 →
≥5% / ≥10% / ≥15% / ≥20% / ≥25–30% responder stacks + T2D, sex, GLP1R genetics & adherence drivers

FIG 4.3 **DXA Body-Composition Partitioning & Lean-Mass Preservation** p. 58 →
~74–75% fat vs ~25–26% lean loss (SURMOUNT-1 DXA) + BELIEVE, T-REx, Exercise BMD & QUALITY RCTs

FIG 6.1 **Within-Trial Dose–Response Curves Across 5 RCTs** p. 95 →
SURMOUNT-1, ATTAIN-1, STEP UP, Retatrutide Phase 2 & Phase 3 TRIUMPH-1

FIG 8.1 **Weight Trajectory After Continuation vs Withdrawal** p. 119 →
STEP 4 & SURMOUNT-4 randomized withdrawal vs STEP 1 observational off-drug extension

FIG 11.1 **Addiction & Cognitive Ratio Estimates by Study Design** p. 175 →
Randomized trial evidence vs non-causal observational cohorts on log ratio scale

TRIPLE-AGONIST, LATE-STAGE PIPELINE & GLOBAL ACCESS PLATES (3)

FIG 13.1 **Investigational Retatrutide Weight Change by Dose** p. 215 →
80-week treatment-regimen estimand in TRIUMPH-1 (no diabetes) and TRIUMPH-2 (T2D)

FIG 14.1 **Late-Stage Incretin, Amylin & Glucagon Pipeline Matrix** p. 242 →
CagriSema REDEFINE, amycretin, petrelintide, eloralintide, MariTide, survodutide & aleniglipron

FIG 16.1 **U.S. Multi-Channel Pricing Waterfall & Global 2030 Access Gap** p. 280 →
$1,028–$1,349 WAC → $245–$299 CMS MFN / $274 MFP → $2.3–$11.7 generic floor + 1.1B global need

How to use this book

How the chapters are built, what the evidence grades mean, and the limits of this reference.

HOW EACH CHAPTER IS BUILT

- A one-line statement of the clinical idea, then focused prose with inline citations [1].
- Evidence chips mark the kind of data behind a claim: human, regulatory, or mechanistic.
- A letter grade (A to D) rates the strength of evidence for the specific use described — not the elegance of the biology.
- KEY POINT boxes carry the practical takeaway; a References list closes each chapter.
- Interactive navigation pills at the top of every page jump directly to Contents, Visuals & Algorithms, the Semaglutide Matrix, the Comorbidity Matrix, and the Trial Glossary.

WHAT THE GRADES MEAN

GRADE	MEANING
A	Consistent randomized trials or meta-analyses for the stated indication.
B	A single high-quality randomized trial, lower-quality trials, or strong observational data.
C	Limited data; mechanism plus small or uncontrolled studies.
D	Very low: preclinical, in vitro, or anecdotal only.

SCOPE AND A DISCLAIMER

Incretin-based therapies are approved for type 2 diabetes and, increasingly, for obesity and a widening set of cardiometabolic, renal and sleep indications, but they are also compounded, sold research-use-only, microdosed, stacked and used off-label on a large scale. This book states where the evidence is strong (weight reduction and glycemic control; cardiovascular, renal and sleep-apnea outcomes

HOW TO USE THIS BOOK · CONTINUED

for specific agents), where it is weak or absent (microdosing, many off-label uses, most peptide stacking), and which agents and uses are investigational. Evidence grades reflect the clinical evidence for the specific indication discussed, not regulatory status or biological plausibility; a warm bar in the left margin marks contraindications, legal prohibitions and unapproved status. The book addresses adults; for pediatric indications (for example, Wegovy injection from age 12), consult the label.

This is educational content for licensed clinicians and a reference for clinical reasoning. It is not medical advice for any individual, does not establish a clinician-patient relationship, and does not replace specialist input or formal guidelines. Approvals, shortage and compounding status, and pipeline data change quickly and differ by country; statements here are dated to 2026. Verify current national sources, and confirm every citation and every dose against the primary literature and the current label before prescribing.

BEFORE YOU START

Keep three categories apart throughout: FDA-approved indications and doses (taken from the current label), off-label uses supported by trial evidence, and investigational or unapproved products. The book gives prescribing regimens only for approved uses. Study doses for off-label or investigational uses appear only where needed to describe the evidence and are identified as trial parameters, not dosing recommendations.

Incretin therapies at a glance

The monograph's core facts in brief.

FIELD	SUMMARY
Drug classes	GLP-1 receptor agonists (the peptide agents exenatide, lixisenatide, liraglutide, dulaglutide and semaglutide, and the oral nonpeptide agonist orforglipron); the dual GIP/GLP-1 agonist tirzepatide; and the investigational triple GIP/GLP-1/ glucagon agonist retatrutide.
Main approved agents	Exenatide, liraglutide (including US generics), dulaglutide, semaglutide (subcutaneous; oral Rybelsus and Ozempic tablets, not mg-for-mg interchangeable, for type 2 diabetes; Wegovy injection and Wegovy 25 mg tablets for weight management), tirzepatide (Mounjaro, Zepbound), and oral orforglipron (Foundayo, approved April 2026).
Lead indications	Type 2 diabetes and chronic weight management. For specific agents, dated through November 2026: cardiovascular risk reduction (semaglutide SC and oral; liraglutide; dulaglutide; tirzepatide in type 2 diabetes, Mounjaro, August 2026), chronic kidney disease in type 2 diabetes (semaglutide SC, FLOW), moderate-to-severe obstructive sleep apnea in obesity (tirzepatide, Zepbound), and noncirrhotic MASH with F2 to F3 fibrosis (Wegovy injection, accelerated approval). Heart failure with preserved ejection fraction with obesity (STEP-HFpEF, SUMMIT), symptomatic peripheral artery disease in type 2 diabetes (STRIDE), and knee osteoarthritis in obesity (STEP 9; investigational retatrutide TRIUMPH-4) have positive phase 3 trial evidence but no standalone FDA indication.
Typical weight effect	Semaglutide 2.4 mg about 15% at 68 weeks (STEP 1); semaglutide 7.2 mg about 19% (STEP UP, intention-to-treat); oral semaglutide 25 mg about 14% at 64 weeks (OASIS 4); tirzepatide up to about 21% at 72 weeks (SURMOUNT-1); oral orforglipron about 11% at 72 weeks (ATTAIN-1); retatrutide up to 25.0% at 80 weeks in the phase 3 TRIUMPH-1 trial (treatment-regimen estimand; investigational). Figures are trial means, not label claims.

INCRETIN THERAPIES AT A GLANCE · CONTINUED

FIELD	SUMMARY
Dosing principle	Weekly or daily injection, or a daily oral tablet; titrate slowly for gastrointestinal tolerability. Oral semaglutide tablets must be taken fasting (empty stomach in the morning with up to 4 ounces of water, then at least 30 minutes before food); orforglipron may be taken at any time with or without food or water. For weight-management products, doses below the approved maintenance range are titration steps, not maintenance regimens; no approved microdosing regimen exists. Wegovy 1.7 mg is itself an approved maintenance dose, and Mounjaro 2.5 mg may remain an on-label T2D dose when additional glycemic control is not needed.
Key safety	Dose-dependent gastrointestinal effects; gallbladder disease; pancreatitis caution. Boxed thyroid C-cell tumor warning and MTC/MEN2 contraindication: liraglutide, dulaglutide, semaglutide, tirzepatide, orforglipron, and extended-release exenatide (Bydureon/Bydureon BCise); not short-acting exenatide (Byetta) or lixisenatide. Class-wide NAION warning (9 Nov 2026): seek urgent ophthalmic evaluation for sudden visual loss; if NAION develops, consider discontinuing the GLP-1 receptor agonist unless the treatment benefit clearly outweighs the risk. Watch for volume depletion and lean-mass/bone loss during rapid weight loss (pair with protein and resistance exercise). Perioperative management is risk-stratified rather than routine cessation.
Stopping therapy	Obesity is chronic and weight/cardiometabolic regain after discontinuation is common at the population level; stopping treatment also removes ongoing exposure to therapies with proven cardiovascular and renal benefits, and in large observational type 2 diabetes cohorts, treatment gaps are associated with higher MACE and all-cause mortality. When therapy is effective and tolerated, long-term maintenance is generally needed.
Regulation	Compounded and 'research-use-only' or 'not for human use' products are sold widely; research-use-only labeling does not make a product lawful for clinical use. The FDA resolved the tirzepatide and semaglutide injection shortages in 2024–2025, and the Fifth Circuit upheld those determinations in August 2026; verify current status against the FDA record.