Polypharmacy and Thermoregulatory Failure: When the Pharmacokinetic Ground Shifts

Heat stroke in the polypharmacy patient is not straightforward hyperthermia. It is the exposure of a pharmacological system calibrated for a body operating at 98.6°F — one now forced to function under conditions of profound physiological stress.

The central problem is that drug behavior is temperature-dependent in ways that accumulate dangerously across a multi-drug regimen. Protein binding, hepatic enzyme kinetics, renal tubular transport, and blood-brain barrier permeability all shift as core temperature rises. A patient stabilized at therapeutic levels on a given morning may, by afternoon at 103°F, be experiencing de facto overdose on the same unaltered dose.

Consider lithium. At normal temperature, renal sodium and lithium reabsorption are coupled in a relatively predictable steady state. As body temperature climbs and insensible fluid losses increase, sodium depletion triggers compensatory proximal tubular lithium retention. Serum concentrations may rise substantially despite no change in prescribed dose. The resulting neurotoxicity — coarse tremor, confusion, ataxia, myoclonic jerks, and altered consciousness — can closely resemble heat encephalopathy itself, delaying recognition of both conditions.

Anticholinergic agents present the inverse problem: they impair sweating at the effector level, converting a manageable heat burden into thermogenic runaway. Tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics can each independently compromise evaporative cooling; in combination, suppression may become clinically significant. Meanwhile, beta-blockers may blunt cardiovascular compensation, while diuretics accelerate volume depletion and electrolyte loss.

Above 104°F, hepatic metabolic pathways become increasingly unreliable as cellular injury, hypoperfusion, and enzyme dysfunction emerge. Drugs dependent upon hepatic clearance may begin to accumulate as metabolic capacity deteriorates in real time. What was a therapeutic plasma concentration at 98.6°F may become toxic as the physiological assumptions underlying drug disposition progressively fail.

The clinical imperative is this: in hyperthermic polypharmacy patients, every drug must be reconsidered as if it were being prescribed for the first time in a chemically altered host. Failure to interrogate the pharmacological implications of hyperthermia in the context of a complex medication regimen constitutes an incomplete clinical response, regardless of the success of thermal intervention.