



# A Birds-Eye (Re)View of Acid-Suppression Drugs, COVID-19, and the Highly Variable Literature

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This *Perspective* examines a recent surge of information regarding the potential benefits of acid-suppression drugs in the context of COVID-19, with a particular eye on the great variability (and, thus, confusion) that has arisen across the reported findings, at least as regards the popular antacid famotidine. The degree of inconsistency and discordance reflects contradictory conclusions from independent, clinical-based studies that took roughly similar approaches, in terms of both experimental design (retrospective, observational, cohort-based, etc.) and statistical analysis workflows (propensity-score matching and stratification into sub-cohorts, etc.). The contradictions and potential confusion have ramifications for clinicians faced with choosing therapeutically optimal courses of intervention: e.g., do any potential benefits of famotidine suggest its use in a particular COVID-19 case? (If so, what administration route, dosage regimen, duration, etc. are likely optimal?) As succinctly put this March in Freedberg et al. (2021), “...several retrospective studies show relationships between famotidine and outcomes in COVID-19 and several do not.” Beyond the pressing issue of possible therapeutic indications, the conflicting data and conclusions related to famotidine must be resolved before its inclusion/integration in ontological and knowledge graph (KG)-based frameworks, which in turn are useful for drug discovery and repurposing. As a broader methodological issue, note that reconciling inconsistencies would bolster the validity of meta-analyses which draw upon the relevant data-sources. And, perhaps most broadly, developing a system for treating inconsistencies would stand to improve the qualities of both 1) real world evidence-based studies (retrospective), on the one hand, and 2) placebo-controlled, randomized multi-center clinical trials (prospective), on the other hand. In other words, a systematic approach to reconciling the two types of studies would inherently improve the quality and utility of each type of study individually.

**Keywords:** COVID-19, histamine (H2) receptor, famotidine, knowledge graph, disease ontology, antagonist action

**Abbreviations:** COD, context of disease; COVID-19, coronavirus disease 2019; DOB, degree of benefit; GPCR, G-protein coupled receptor; KG, knowledge graph; MOA, mechanism/mode of action; RDF, resource description framework; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

## INTRODUCTION: POSSIBLE SYSTEMATIC APPROACHES?

To begin systematically structuring the rapidly accumulating information on COVID-19 (Triggle et al., 2021)—in the hopes of clarifying and reconciling the discrepancies, and eventually maturing the information into *clinically-actionable knowledge and understanding*—let us view this topic along three “axes” implied by our opening sentence: namely, we consider 1) a *context-of-disease* (COD) axis, 2) a *degree-of-(therapeutic)-benefit* (DOB) axis, and 3) a *mechanism-of-action* (MOA) axis. We now treat each of these in turn; note that these “axes” are of *nominal* type, in terms of classification levels and typologies (Stevens, 1946).

The *MOA axis* may be the most straightforward to conceptualize, as it simply describes the MOA of a putative drug—i.e., the mechanistic, molecular-level etiological basis (to the extent known), in whatever might be the most salient pharmacological pathways for that compound. As a concrete example, known gastroenterological acid-suppression agents may act either: 1) as proton-pump inhibitors (PPIs), sterically occluding proton efflux via the  $H^+/K^+$ -ATPase pumps that mediate the final step of acid release in the gastric mucosa, or 2) as histamine type-2 receptor antagonists (H2RAs), whereby specific binding to this subtype of G-protein coupled receptor blocks the downstream signaling and effector cascades that otherwise would have been triggered by the cognate ligand, i.e., histamine (Eldanasy et al., 2020; Ennis and Tiligada, 2021). An example of a widely used PPI is omeprazole (e.g., Prilosec®), and famotidine (e.g., Pepcid®) and ranitidine (e.g., Zantac®) are examples of popular over-the-counter H2RAs. In the context of our present example, the MOAs of these two particular classes of GI drugs are mutually exclusive—i.e., a drug  $\mathcal{D}$  acts by one pathway  $\mathcal{P}_1$  (PPI-blocker) or another  $\mathcal{P}_2$  (H2RA), but not both. Such basic, molecular-level selectivity is not always the case, and, indeed, the approach of polypharmacology (Xie et al., 2012) relaxes the rigidity of the “one gene, one disease, one drug” view by recognizing that, *in vivo*, a given drug compound likely has multiple targets in multiple physiological pathways; indeed, generally speaking the potential multiplicity of drug-target linkages can be leveraged to beneficial effect. Further consideration of “off-target” effects (beneficial or detrimental) is beyond the scope of our present treatment. Here, we only note that a recent study (Malone et al., 2021) offers a detailed and insightful analysis of possible on-/off-target properties of famotidine, particularly as regards 1) hypothesis testing of its MOA, and 2) discrepancies that can arise among different studies because of differences in dosage, single- and multi-agent treatment regimes, pharmacokinetic-related properties (e.g., ADME), and so on; notably, that work concluded that off-target (i.e., non-H2R) pathways likely do not play a major role in the case of famotidine as a potential COVID-19 therapeutic.

One can envision developing more quantitative descriptors of the entities that populate the MOA axis and their interrelationships (to move from our nominal scale towards something more like an *ordinal scale*) by employing

approaches such as the *Coronavirus Infectious Disease Ontology* (Liu et al., 2021) to represent the targets of  $\mathcal{D}$  in the  $\mathcal{P}_1, \mathcal{P}_2$ , etc. pathways, the possible side-effects, and so on. [Note that *CIDO* is one of many biomedical ontologies gathered at *BioPortal* (Whetzel et al., 2011).] A potential source of confusion in the recent famotidine literature, taken in totality, is that recent meta-analyses (Sethia et al., 2020b; Kamal et al., 2021; Sun et al., 2021) of retrospective, observational, cohort-based studies have not always enforced a clean delineation between the two MOAs mentioned above (i.e., PPI, H2RA), at least when drawing their conclusions. As a case in point, some primary studies have found that famotidine is beneficial whereas PPIs offered “no protective effect” (Freedberg et al., 2020a); another study found no positive effect of famotidine and also no deleterious effect of PPIs (Elmunzer et al., 2020); another found no association between PPIs and a different H2RA (ranitidine), in terms of likelihoods of both COVID-19 infection and death (Fan et al., 2021); a pair of studies found no evidence for additional risks or benefits, for neither famotidine nor PPIs (Cheung et al., 2020; Shoaibi et al., 2021); and, finally, another recent study (Zhou et al., 2020) found greater risks of association with morbidity or severe illness for famotidine and PPIs (each one, individually). Such incongruities, viewed holistically across all of the studies, result in internal inconsistencies when meta-analyses then draw upon a set of such studies: there is no clear “combining” rule to harmonize otherwise inconsistent data sources and data values. Also, in some sense, comparing drugs with different MOAs, under the umbrella of a single, global analysis (be it a meta-analysis or a manual/human-expert analysis), is akin to comparing apples and oranges: they are of fundamentally different *types*, and attempts to compare them are *ill-posed* in the ontological sense of semantic networks, structured reasoning, KGs, and so forth [reviewed in Kanza and Frey (2019)]. From a pharmacogenomics and drug discovery perspective, a key goal would be the development of ontology-based knowledge representation graphs (or *semantic models*) of the cellular pathways wherein famotidine might intervene pharmacologically (Figure 1). Such an approach could enable systematic, automated discovery—*via reasoning* over the graph—of potential new targets, new drug leads, and prediction of new drug/target pairs (using existing software systems and toolkits); however, constructing such a framework would require resolution of inconsistencies among the primary data used to build the semantic network’s relationships (Figure 1A).

A few studies have begun considering the possible sources of discrepancies and heterogeneities, to which at least some of the inconsistencies in the famotidine/COVID-19 literature can be attributed. Some such sources relate to differences in study designs, or are otherwise methodological in nature—e.g., Freedberg et al.’s (2020b) description of potential biases from residual confounders in the baseline characteristics of case-matched cohorts. There also exists the possibility of spurious links (or, inversely, masked associations) because of underlying physiological factors, e.g., Sethia et al.’s (2020a) description of the impacts of 1) potentially great differences in disease severity on treatment outcomes (without adequately accounting for such in case-matching and stratification methods to obtain sub-cohorts),



[e.g., lansoprazole as an inhibitor of rhinovirus infection (Sasaki et al., 2005)], yet they may not be necessarily beneficial in treating COVID-19. Idiosyncratic patterns such as these are drug-specific, pathway-dependent and disease-related, and they are especially salient in drug repurposing efforts [an endeavor that was recently reviewed for COVID-19 in Tarighi et al. (2021), and by Aguila and Cua (2020) for the particular case of GI drugs; such repurposing efforts are facilitated by modern web-based resources, e.g., PROMISCUOUS (Gallo et al., 2021)].

The *context-of-disease* (COD) axis accounts for the fact that, in addition to being subjective, the term “beneficial” is also vague: it can be gauged by various *types* of outcomes/criteria, even for a single disease or given set of indications. In the context of COVID-19 and other infectious diseases, a putative drug may be “beneficial” as regards its impact upon 1) *transmissibility*, e.g., Fan et al. (2021) considered if usage of the H2RA ranitidine modulates susceptibility to SARS-CoV-2 infection; 2) *disease severity* indicators, e.g., the likelihood of cases reaching the point of mechanical ventilation, the WHO Severity Index [Yeramaneni et al. (2021) used this ordinal scale in their COVID-19 study], or other measures; and 3) *mortality rates*, frequencies or related metrics. Unlike the MOA axis the entities along the COD axis can overlap, at least in our current example of COVID-19 and acid-suppressing drugs—for example, there is no a priori reason why a given drug cannot be beneficial in two senses, e.g., by diminishing transmissibility of SARS-CoV-2 and by reducing the severity of the disease trajectory once it has been contracted [note, though, that in general different cellular/molecular-scale pathways (MOAs) can underlie similar organismal-level outcomes].

We suspect that some incongruities in how these MOA, COD and DOB axes have been (implicitly) treated in the various, independent studies is what has led to the contradictory indications regarding famotidine and COVID-19 (*anti-famotidine*, *neutral*, *pro-famotidine*) in the published literature. Harmonizing the findings across the literature is an important goal from the perspectives of both bioinformatics and clinical standards-of-care/best practices for a given disease.

## HAS OUR UNDERSTANDING PROGRESSED?

Finally, now to trace the evolution of what we know about the potential benefits (DOB) of H2RAs, PPIs, etc. (different MOAs) on the transmission, severity, and mortality (various CODs) of COVID-19, let us consider the many literature reports that have accumulated in the past year. By grouping these studies conceptually and thematically we can begin to identify the following three “Eras” in the progression of the literature (and our understanding) as regards famotidine and COVID-19:

- *Era 1: Primary research studies by independent groups*: These ≈10 analyses generally have been *retrospective*, *observational* (some *cohort-based*, some *case-series*) and *single-site/center*. Most of the studies attempted to *statistically adjust for confounders* (e.g., *via* propensity score matching), though with varying degrees of rigor and caution (see the study cited in *Era 3*, below). Despite many similarities in design, there have emerged two contradictory sets of studies: 1) several studies concluded in favor of using famotidine in COVID-19 i.e., Freedberg et al. (2020a), Janowitz et al. (2020), Mather et al. (2020) and Hogan et al. (2020), while 2) a roughly equal number did not, i.e., Cheung et al. (2020), Elmunzer et al. (2020), Zhou et al. (2020), Fan et al. (2021) and Yeramaneni et al. (2021). In the second category of reports which were less enthusiastic about famotidine, some did suggest against the usage of famotidine (Cheung et al., 2020; Yeramaneni et al., 2021; Zhou et al., 2020), while others found no association for famotidine or PPIs and COVID-19 therapeutic value (Elmunzer et al. (2020) and Fan et al. (2021)).
- *Era 2: Meta-analyses of the primary literature reports*: Three such analyses have appeared thus far, with again varying results: Sethia et al. (2020b) were cautiously pro-famotidine, while Sun et al. (2021) and Kamal et al. (2021) were more neutral/negative, determining for the most part that no association (positive or negative) was statistically justifiable. Why the inconsistency in whether or not famotidine is indicated for COVID-19, even at the level of a meta-analysis? One contributing factor could be that different database inclusion criteria were used in these different meta-analyses (cf. Methods sections in each of these three studies). For instance, Sun et al. (2021) drew upon several Chinese databases and did not sample the medRxiv or SSRN preprint collections, whereas Sethia et al. (2020b) included medRxiv and SSRN but not the several Chinese databases. This could be a source of discrepancy between the meta-analyses. Furthermore, it is perhaps unsurprising that the meta-analysis which did reach a more favorable conclusion as regards indicating famotidine (i.e., Sethia et al.) leaned most heavily on studies from the primary literature which were, themselves, most strongly in favor of famotidine on average (see those cited in *Era 1*, above); in contrast, the meta-analysis which found no/less-favorable association between famotidine and positive COVID outcomes (i.e., Sun et al.) included a subset of case/cohort-studies that generally reached less favorable conclusions [e.g., Cheung et al. (2020); Shoaibi et al. (2021); Yeramaneni et al. (2021)]. The third meta-analysis, of Kamal et al. (2021), does not serve as a “tie-breaker” here, as it finds a “lack of consistent association” between COVID-19 outcomes and the use of acid-suppression drugs (for both famotidine and PPIs). Finally, as can generally occur in bibliometric meta-analyses, a “positive-outcome” publication bias (Fanelli, 2012) may exist in the data sources, with negative findings never having made it to the primary, peer-reviewed literature.
- *Era 3: Origins of the discrepancies?* Without resorting to a *meta-meta-analysis*(!), Etminan et al. (2020) recently supplied a thorough and incisive critique of factors that may limit the consistency of the conclusions drawn thus far from the primarily retrospective, observational, single-site



studies, such as those in Elmunzer et al. (2020), Freedberg et al. (2020a) and Mather et al. (2020). In particular, likely sources were identified for several types of biases, including residual *confounding bias* and *sparse-data bias*, *immortal time bias* (and somewhat related *selection bias* effects), and reverse causality bias [the latter can be understood *via causal directed acyclic graph* (cDAG) models, which can elucidate the structure of these epidemiological biases]. Here, we simply note that: 1) Some of these sources of bias are rather more difficult to control for, or statistically identify and account for, than others (because of causal relationships, limited data, etc.); 2) In principle, biases, in and of themselves, do not necessarily result in inconsistencies among a series of primary research studies. That is, *bias* and *inconsistency* are not equivalent phenomena: conceivably, each study within a series of studies could suffer from similar biases, and nevertheless still be self-consistent. Regardless, Etminan et al. highlight several improvements that can be made in future approaches to statistically elucidate famotidine ↔ COVID-19 relationships.

## DISCUSSION

Perhaps some inconsistencies can be resolved by viewing famotidine and its potential roles in COVID-19 through a more mechanistic, molecular-level lens? Alongside the observational, patient-based studies, the potential MOA for a therapeutic role of famotidine has been explored in a few publications. In particular, a recent review by Ennis and Tiligada (2021) offers a cogent and authoritative treatment of the connection between histamine receptor antagonists (e.g., famotidine) and COVID-19, while histamine release theory was also the subject of accounts by Eldanasory et al. (2020) and Ghosh et al. (2020) regarding the role of this versatile signaling molecule in pro-inflammatory pathways—including the destructive “cytokine storm” that appears to underlie much of the pathophysiology of COVID-19, at least with respect to pulmonary consequences (fibrosis, etc.) and the resultant acute respiratory distress. More generally, famotidine and other GI-related drugs appear in a comprehensive review by Tarighi et al. (2021) of drug repurposing in the age of COVID, and a recent letter by Singh et al. (2020) considered the question of what (molecularly) underlies the efficacy of treatment of COVID with famotidine? These mechanistic, biomolecular directions offer hope, as it is often the case that multiple disparate (and seemingly contradictory) phenomena, or sets of observations, at a macroscopic/organismal level become reconciled when viewed at the molecular level—i.e., by appealing to the underlying cellular and physiological pathways. Indeed, we suspect that the reconciliation and harmonization of independent, contradictory findings, such as for famotidine and COVID-19, ultimately will lie along two paths: 1) molecular-level examination of whatever pathways are thought to be most salient for the macroscopic phenomena of interest (clinical-level observations), and 2) multi-scale, integrative modeling of

the interaction and build-up of microscopic phenomena (e.g., drug-protein interactions) through many hierarchical levels (organellar → subcellular → cellular → tissues → ...) up through to the organismal level, and eventually even populations (therapeutic outcomes, like altering the course of an infection).

## ONTOLOGIES, AND A WAY FORWARD?

A key motivation for reconciling conflicts in the famotidine × COVID-19 literature, in terms of basic drug discovery/repurposing and modeling COVID-19-drug interactions, stems from the importance of data consistency and harmonization in creating ontology-based knowledge graphs of biomolecular systems. **Figure 1** schematizes the types of *Resource Description Framework* (RDF) “triples” used to express the relationships between distinct entities in an ontology [Andronis et al. (2011), Blake (2013), and Hastings (2017) offer introductions/primers on ontologies]. The example in **Figure 1** also denotes other histamine receptors (H1R, H3R, H4R) in order to emphasize that any given pairwise relationship does not exist in isolation: all simpler relationships are embedded within physiological contexts that typically involve many entities (with varying degrees of confidence in the linkages). While RDF triples capture relationships between entities, the other aspect of an ontology is a higher-level *structuring* or *organization* (typically hierarchical) for the collection of classes/concepts (of which a given entity is an *instance*) that span the ontology’s domain of knowledge. A gene ontology [GO; Ashburner et al. (2000)] “ancestor chart”, shown in **Figure 1B**, illustrates such a concept hierarchy for the term GO:0031808, corresponding to H2R-binding. The excerpt of a host–coronavirus drug/interactions map (**Figure 1C**) is a graph-based representation that reflects both aforementioned aspects of an ontology, namely 1) the *structural interrelationships* among concepts/entities (some broad, some specific, some subsets of others, etc.) as well as 2) the *pairwise associations* (RDF triples) from which such KGs are built. These “semantic network” approaches are compelling and powerful for many reasons [reviewed in Andronis et al. (2011) and Kanza and Frey (2019)], including that the KG can be used for drug discovery, pharmacogenomics modeling, and “big data” endeavors (data integration across scales); one manner in which this is achieved is by “reasoning” over the KG, beyond the initial confines (or domain) of the data sources. The success of all such efforts rests upon the data being systematized against a controlled vocabulary, syntactically well-formed, and so on. A key determinant of our ability to build such graphs is that there not be internal inconsistencies, such as “ $\sqrt{Famo_{DOB}^{COVID}}$ ” and “ $\times Famo_{DOB}^{COVID}$ ”. Resolving inconsistencies and inaccuracies in the data-sources can mitigate the “percolation” of such errors through the graph, thereby limiting potentially erroneous downstream conclusions (such conclusions are often reached by applying machine learning approaches to perform statistical inference on the graph-based structures).

Together with the findings from several sets of prospective clinical trials that have been underway—including NCT04504240, NCT04370262 and NCT04545008 in the United States, and other efforts internationally [e.g., Samimaghani et al. (2020)]—we anticipate that detailed

biomolecular studies can help clarify the contradictory relationships that have been reported thus far between famotidine and COVID-19. That, in turn, will enable the creation of more robust, efficacious and predictive ontological frameworks for drug discovery and pharmacological repurposing.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

Conception and design: CM Acquisition, analysis and interpretation of data: CM, SP, RP, and PB Drafting of the

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