birds

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Review

A Critical Review of the Pharmacokinetics and Pharmacodynamics of Opioid Medications Used in Avian Patients

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Simple Summary: In administering opioid medications for a particular species of bird, doses are usually extrapolated from other species of birds. This is unideal as differences in the physiology of birds, even among closely related species, may affect drug action and disposition, and hence the efficacy and safety of drugs used. We collated opioid dosing regimens used in birds from the literature and evaluated their efficacy, safety and pharmacokinetic data. Tramadol, hydromorphone, buprenorphine, butorphanol and fentanyl were found to be generally safe. However, there was a lack of analgesic effects for hydromorphone and buprenorphine in Cockatiels (*Nymphicus hollandicus*). American Kestrels (*Falco sparverius*) appeared to exhibit sex-dependent responses to opioids. Differences in the bioavailability of oral tramadol was seen between Hispaniolan Parrot (*Amazona ventralis*) and Bald Eagle (*Haliaeetus leucocephalus*).

Abstract: Opioid drugs are used to manage moderate to severe pain in mammals and avian species. In dosing opioids for a particular species, it is optimal to use dosing regimens based on pharmacokinetics or pharmacodynamics studies conducted in the same species as variability in the physiology among different species may result in differences in drug pharmacokinetics and pharmacodynamics. Unfortunately, dosing regimens are typically extrapolated from closely related avian species or even mammals, which is unideal. Therefore, this critical review aims to collate and evaluate the dosing regimens of selected opioids: tramadol, hydromorphone, buprenorphine, butorphanol, and fentanyl, in avian species and its related safety, efficacy and pharmacokinetic data. Our review found specific dosing regimens not described in the Exotic Animal Formulary for tramadol used in Indian Peafowl (*Pavo cristatus*), Muscovy Duck (*Cairina moschata*) and Hispaniolan Parrot (*Amazona ventralis*); hydromorphone used in Orange-winged Parrot (*Amazona amazonica*); buprenorphine used in Cockatiel (*Nymphicus hollandicus*), American Kestrel (*Falco sparverius*) and Grey Parrot (*Psittacus erithacus*); and butorphanol used in Hispaniolan Parrot (*Amazona ventralis*), Broiler Chicken and Indian Peafowl (*Pavo cristatus*). Cockatiel appeared to not experience analgesic effects for hydromorphone and buprenorphine, and American Kestrel exhibited sex-dependent responses to opioids. The selected opioids were observed to be generally safe, with adverse effects being dose-dependent.

Keywords: opioids; tramadol; hydromorphone; buprenorphine; butorphanol; fentanyl; birds; avian; pharmacokinetics; dosing

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1. Introduction

There are 10,806 extant species of birds in the world, which are classified to 40 orders, 252 families and 2353 genera [1]. 20.6 million birds were owned as companion in the United States households and 6% of pet owners in Singapore owned pet birds in 2017 and 2018, respectively [2,3], making birds important for their sentimental value to humans. Birds are also important as they are featured in zoos and parks, as well as for their value in nature conservation.

In efforts to conserve bird species or keeping them as pets, birds may experience potentially painful injuries, diseases or surgical procedures. Alleviating pain in birds may not be as straightforward as doing so in humans as they are unable to express pain effectively through facial or verbal expressions. There could also be situations where birds potentially experience pain, but do not show any behavioral or facial changes. Even when behavioral changes in birds potentially experiencing pain are present, they could still be difficult to assess as this requires the observer to be able to recognize the full range of normal and abnormal behaviors of each species and individual to assess pain. There are also other factors to be considered when assessing pain in birds, including age, species, gender, environment, strain, and breed [4,5]. Therefore, if any of the points above hold true, veterinarians must assume that the animals are in pain and development of an analgesic plan is deemed necessary if:

(A) The lesion or procedure would be painful to other species;
(B) The lesion or procedure is damaging to tissues in other species;
(C) The patient shows any abnormal behaviour [4].

Providing appropriate analgesia is an important aspect of veterinary care in all species, including avian species, that are going through potentially painful experiences or procedures. Other than the moral obligation to provide analgesic plans in managing potentially painful injuries in birds, there are also other reasons to manage pain in birds. Injury may cause an animal to be immobilized, resulting in muscle weakness and wasting [6]. Arthritis-induced Muscovy Duck (*Cairina moschata*) in the control arm had a greater difference in maximum force on left and right legs as compared to those treated with pain-relieving drugs such as meloxicam and tramadol, indicating lameness on the arthritis-induced leg [7]. This indicates that relieving pain is important in maintaining mobility of birds. Furthermore, poorly treated pain can result in self-mutilation or lead to chronic pain syndromes. Birds may resort to damaging behaviors such as feather picking [8]. This may result in reduced aesthetic in birds, reduced ability to keep themselves warm and dry, as well as an increased exposure to skin infections or other complications [8,9].

Opioid drugs, in veterinary medicine, are used for moderate to severe pain such as in fractures or surgery [4]. Generally, the Exotic Animal Formulary (EAF) is used as a reference for dosing regimen of specific opioid drugs [10]. However, there is a lack of dosing regimens of opioids in selected species of birds. Thus, when data is unavailable for selected species of birds, doses are often extrapolated from closely-related bird species or other animal species [11–14]. However, interspecies variability in terms of the anatomy and physiology is present even between closely-related bird species. This may translate to differences in drug pharmacokinetics (PK) and/or pharmacodynamics (PD), resulting in differences in the safety and efficacy, when the same drug dosing regimen is administered across different species [11]. For example, in studies evaluating the analgesic effects of butorphanol using the isoflurane-sparing technique, 1 mg/kg of butorphanol was found to be analgesic in Cockatoos (*Cacatua galerita*, *Cacatua sulphurea cintrinocristata*, *Cacatua sulphurea sulphurea*), but not Hispaniolan Parrot (*Amazona ventralis*) [5] These results highlight variations in drug PK and PD between species, even among the closely-related psittacine species. Therefore, intraspecies scaling of dosing regimen in a particular species of birds is unideal [12–14].

In mammals, analgesia is achieved when opioids bind to either μ-, κ-, or δ-opioid receptors in the central nervous system (CNS), either spinally or supraspinally [4]. The opioids are categorized as agonists, partial agonists, mixed agonist/antagonists or antagonists. This categorization depends on each opioid's ability to induce analgesic response when bound to a specific receptor. The agonists have a linear dose-response curve, whereby dose can be increased to achieve the desired effect. On the other hand, mixed agonist/antagonist opioids may have agonist property to one receptor but act as antagonist at another type of receptor. Agonist/antagonist opioids may reach a plateau in terms of its analgesic effect, where increasing the dose does not provide additional analgesia [15].

Besides analgesia, opioids are often used in mammals during anesthesia to provide the anesthesia-sparing effect, where use of opioids may reduce the concentration of volatile

anesthetics required [6]. In birds, opioids can also be used to provide the anesthesia-sparing effect [16–18].

Opioid analgesics commonly used in birds are those that act on μ- or κ-opioid receptors. This critical review will discuss these opioids, particularly on tramadol, hydromorphone, buprenorphine, butorphanol and fentanyl. Table 1 summarizes the interactions of selected opioids with μ- or κ-opioid receptors.

Table 1. The interactions of selected opioids with μ- or κ-opioid receptors and their classification.

Opioid	Interaction with μ-Opioid Receptor	Interaction with κ-Opioid Receptors
Tramadol [19]	Weak agonist	-
Hydromorphone [20]	Agonist	-
Buprenorphine [21]	Partial agonist-antagonist	-
Butorphanol [22]	Mixed agonist/antagonist	Partial agonist
Fentanyl [23]	Agonist	-

Therefore, this critical review aims to collate evidence of the dosing regimens of opioids used in different avian species, evaluate their safety and efficacy data, and identify any trends in the PK of the opioids in the different avian species.

2. Methods

Articles were searched on PubMed (https://pubmed.ncbi.nlm.nih.gov/) accessed on 30 January 2021 using keywords related to the concept of birds, opioids, and pharmacokinetic (PK) and pharmacodynamic (PD). The full list of keywords can be found in Table A1. Efficacy and adverse effects were not searched for, but were recorded if data was found in the included papers. For a paper to be included, it had to provide either PK or PD information on the opioid used in particular species of birds. PD information is related to how the bird reacts to antinociceptive stimulus such as thermal or electrical. Data extracted included: name of species, weight and age of species, sample size, dosing regimen, half-life, C_{max}, bioavailability, duration mean plasma concentration exceeding target plasma concentration considered analgesic in other animals/human, adverse effects and dosing recommendation.

3. Overview of Dosing Regimens of Opioids Used in Avian Species

This section provides information on dosing regimens of selected opioids studied in various species of birds. It also identifies dosing regimens not found in the EAF 5th edition. Dosing regimens recommended by EAF are generally dosing regimens that have been studied or are subsets of what was studied. However, there were a few exceptions whereby the dosing regimens recommended by EAF were higher or lower than the dosage studied, which will be highlighted in Table 2. Specific dosing regimens not described in EAF was found for tramadol used in Indian Peafowl (*Pavo cristatus*), Muscovy Duck (*Cairina moschata*) and Hispaniolan Parrot (*Amazona ventralis*); hydromorphone used in Orange-winged Parrot (*Amazona amazonica*); buprenorphine used in Cockatiel (*Nymphicus hollandicus*), American Kestrel (*Falco sparverius*) and Grey parrot (*Psittacus Erithacus*); and butorphanol used in Hispaniolan Parrot (*Amazona ventralis*), Broiler Chicken (*Gallus gallus domesticus*) and Indian Peafowl (*Pavo cristatus*). The details of the dosing regimens are shown in Table 2.

Table 2. Dosing regimens of selected opioids studied in various species of birds.

Drug	Species (English Name)	Species (Scientific Name)	Route of Administration	Age (Years)	Duration of Treatment	Dosing Regimen Studied	Dosing Regimen Found in Exotic Animal Formulary 5th Edition (Yes/No)	Reference
Tramadol	Bald Eagle	*Haliaeetus leucocephalus*	Oral	-	Single dose	11 mg/kg [1]	Yes	[24,25]
			Intravenous	-	Single dose	4 mg/kg [2]		
	American Kestrel	*Falco sparverius*	Oral	3	Single dose	5 mg/kg 15 mg/kg 30 mg/kg	Yes	[26]
	Red-tailed Hawk	*Buteo jamaicensis*	Oral	-	Single dose	11 mg/kg [3]	Yes [4]	[25,27]
	Jackass Penguin	*Spheniscus demersus*	Oral	1.5–20	Single dose	10 mg/kg	Yes	[28]
	Hispaniolan Parrot	*Amazona ventralis*	Oral	-	Repeated dose (BD) for 5 days	30 mg/kg	Yes	[29–32]
			Intravenous	-	Single dose	5 mg/kg	No	
	Indian Peafowl	*Pavo cristatus*	Oral	-	Single dose	7.5 mg/kg	No	[33]
	Muscovy Duck	*Cairina moschata*	Oral	-	Single dose	30 mg/kg	No	[7,34]
Hydromorphone	American Kestrel	*Falco sparverius*	Intramuscular	2	Single dose	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Yes	[35,36]
	Cockatiel	*Nymphicus hollandicus*	Intramuscular	2–6	Single dose	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Yes	[37]
	Orange-winged Parrot	*Amazona amazonica*	Intramuscular	4–17 and 28–45	Single dose	0.1 mg/kg 1 mg/kg 2 mg/kg	No [5]	[38,39]
			Intravenous	28–45	Single dose	1 mg/kg	No	
Buprenorphine	Grey Parrot	*Psittacus erithacus*	Intramuscular	-	Single dose	0.1 mg/kg	Yes [6]	[40,41]
			Intravenous	-	Single dose	0.1 mg/kg	No	
	American Kestrel	*Falco sparverius*	Intramuscular	3	Single dose	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Yes	[42,43]
			Intravenous	3	Single dose	0.6 mg/kg	No	
			Subcutenous (sustained-release)	3–5	Single dose	1.8 mg/kg	Yes	[44,45]
			Intramuscular (sustained-release)	3–5	Single dose	1.8 mg/kg	Yes	
	Red-tailed Hawk	*Buteo jamaicensis*	Intramuscular	-	Twice daily	0.25 mg/kg	Yes	[46]
			Subcutaneous (concentrated)	-	Single dose	0.3 mg/kg 1.8 mg/kg	Yes	[47]
	Rock Dove	*Columba livia*	Intramuscular	-	-	Unable to find evidence	Yes	[10]
	Cockatiel	*Nymphicus hollandicus*	Intramuscular	2–6	Single dose	0.6 mg/kg 1.2 mg/kg 1.8 mg/kg	No [7]	[48]
Butorphanol	Hispaniolan Parrot	*Amazona ventralis*	Oral	8	Single dose	5 mg/kg	No	[49]
			Intravenous	8	Single dose	5 mg/kg	Yes	
			Intramuscular	8	Single dose	2 mg/kg [8] 5 mg/kg	Yes	[49,50]
			Subcutaneous (long-acting)	-	Single dose	12 mg/kg	No	[51]
			Subcutaneous (liposome-encapsulated)	11–27	Single dose	10 mg/kg 15 mg/kg	No	[50,52]
	Grey Parrot and Timneh Parrot	*Psittacus erithacus and Psittacus timneh*	Intramuscular	-	Single dose	1 mg/kg	Yes	[41]
	Red-tailed Hawk	*Buteo jamaicensis*	Intravenous	-	Single dose	0.5 mg/kg	Yes	[53]
			Intramuscular	-	Single dose	0.5 mg/kg	Yes	
	Great Horned Owl	*Bubo virginianus*	Intravenous	-	Single dose	0.5 mg/kg	Yes	[53]
			Intramuscular	-	Single dose	0.5 mg/kg	Yes	
	American Kestrel	*Falco sparverius*	Intramuscular	2–3	Single dose	1 mg/kg 3 mg/kg 6 mg/kg	Yes	[54]

Table 2. *Cont.*

Drug	Species (English Name)	Species (Scientific Name)	Route of Administration	Age (Years)	Duration of Treatment	Dosing Regimen Studied	Dosing Regimen Found in Exotic Animal Formulary 5th Edition (Yes/No)	Reference
	Sulphur-crested Cockatoo and Yellow-crested Cockatoo	*Cacatua galerita, Cacatua sulphurea citrinocristata and Cacatua sulphurea sulphurea*	Intramuscular	-	Single dose	1 mg/kg	Yes	[16]
	Psittacine	-	Constant-Rate Infusion	-	-	Unable to find evidence	Yes [9]	[10]
	Ratite	-	Intravenous	-	-	Unable to find evidence	Yes [10]	[10]
	Broiler Chicken	-	Intravenous	-	Single dose	2 mg/kg	No	[55]
	Indian Peafowl	*Pavo cristatus*	Osmotic pump	-	7 continuous days	120 µg/kg/hr with rate 48.1 mg/mL [11]	No	[56]
Fentanyl	African and New World Parrots	*Cacatua alba*	Intramuscular	-	Single dose	0.01 mg/kg 0.02 mg/kg	Yes	[57]
			Subcutaneous	-	Single dose	0.2 mg/kg	Yes [12]	
	Red-tailed Hawk	*Buteo jamaicensis*	Constant-Rate Infusion	-	-	Unable to find evidence [13]	Yes	[10]
	Hispaniolan Parrot	*Amazona ventralis*	Constant-Rate Infusion	-	-	Unable to find evidence [14]	Yes	[10]
	Helmeted Guineafowl	*Numida meleagris*	Transdermal	-	Single dose	5 mg/kg	No	[58]
	Chickens (Brahma, Delaware, Redstar and Wyandotte)	-	Transdermal	3	Single dose	25 µg/h for 72 h	No	[59]

[1] Dosing regimen recommended by both author and Exotic Animal Formulary 5th edition is 5 mg/kg q 12 h. Recommendation is based on simulation in the stud. [2] Dosing regimen recommended in Exotic Animal Formulary 5th edition is 5 mg/kg, which is higher than dosage studied. [3] Dosing regimen recommended by author is 15 mg/kg q 12 h. Recommendation is based on simulation. [4] Dosing regimen recommended in Exotic Animal Formulary 5th edition is 8–11 mg/kg. [5] Exotic Animal Formulary 5th edition was available online in November 2017 but Pharmacokinetics and Pharmacodynamics papers were published in 2020. [6] Dosing regimen in Exotic Animal Formulary 5th edition also includes 0.25 mg/kg, which is not studied. [7] Paper was published in December 2018 while Exotic Animal Formulary 5th edition was available online in November 2017. [8] This study shows butorphanol as an effective pre-emptive analgesia with sevoflurane anesthesia. [9] Exotic Animal Formulary 5th edition dosing regimen recommendation of constant-rate infusion butorphanol in psittacine is 3 mg/kg (premedication) + 75 µg/kg/min IV CRI (maintenance). [10] Exotic Animal Formulary 5th edition dosing regimen recommendation of Intravenousbutorphanol in ratites is 0.05–0.25 mg/kg. [11] Infusion rate = target plasma butorphanol concentration ×Cl = 60 µg/L × 2 L/kg/h = 120 µg/kg/h. Required concentration = infusion rate × bird's body weight/temperature-adjusted pump rate = 120 µg/kg/h × 4.45 kg/11.1 µL/h = 48.1 µg/µL = 48.1 mg/mL. [12] Dosing regimen recommendation in Exotic Animal Formulary 5th edition is 0.1 mg/kg, which is lower than dosage studied. [13] Exotic Animal Formulary 5th edition dosing regimen recommendation of CRI fentanyl for Red-tailed Hawk is 20 µg bolus + 0.2–0.5 µg/kg/min. [14] Exotic Animal Formulary 5th edition dosing regimen recommendation of CRI fentanyl for Red-tailed Hawk is 20 µg bolus + 1.5–6 µg/kg/min.

4. Evaluation of Dosing Regimens in Relation to Efficacy Evidence

The efficacy data for selected opioids administered to bird species studied are reflected in Table 3. PD studies selected were those which provided information on foot withdrawal thresholds to thermal or electrical stimuli after administration of selected opioids. A significant increase in foot withdrawal threshold to thermal or electrical stimuli after the administration of an opioid indicates the analgesic effect of the opioid used for the particular type of pain. PD studies may also utilize arthritis-induced birds. However, when PD studies were unavailable, PK studies were used to determine whether plasma concentrations of the selected opioids reached the target concentration. This target concentration is usually derived from plasma concentration of opioids associated with analgesia in humans with the exceptions of hydromorphone and butorphanol, where plasma concentrations associated with analgesia in American Kestrel and Hispaniolan Amazon were used, respectively. This plasma concentration was derived from PK and PD studies involving the administration of liposome-encapsulated butorphanol in Hispaniolan Amazon [50,52].

Table 3. Efficacy of selected opioids based on pharmacodynamics studies and plasma concentrations.

Species Name		Dosing Regimen		PD Study			Plasma Concentration				
English	Scientific	Dose	Administration	Type	Result	Duration	Target (Parent/Metabolite)	Source	Duration ≥ Target Concentration		Reference
									Opioid	Metabolite	
TRAMADOL											
Bald Eagle	*Haliaeetus leucocephalus*	11 mg/kg	Oral	-	-	-	298–590 ng/mL/39.6–84 ng/mL	Human	10 h; 5/6 birds	2 eagles; 1 timepoint each	[24,25]
		4 mg/kg	Intravenous	-	-	-	298–590 ng/mL/39.6–84 ng/mL	Human	5 h; 5/6 birds	-	
American Kestrel	*Falco sparverius*	5 mg/kg 15 mg/kg 30 mg/kg	Oral	Thermal stimulus	Significant increase in thermal withdrawal threshold.	9 h for 5 mg/kg; 3 h for 15 mg/kg and 30 mg/kg.	-	-	-	-	[26]
Red-tailed Hawk	*Buteo jamaicensis*	11 mg/kg	Oral	-	-	-	298–590 ng/mL/39.6–84 ng/mL	Human	4 h after dosing	-	[25,27]
Jackass Penguin	*Spheniscus Demersus*	10 mg/kg	Oral	-	-	-	298–590 ng/mL/39.6–84 ng/mL	Human	12 h in 9/15 of birds and 24 h in 1/15 of birds	36 h in 14/15 of birds	[28]
Hispaniolan Parrot	*Amazona ventralis*	30 mg/kg	Oral	Thermal stimulus	Significant increase in thermal withdrawal threshold	-	298–590 ng/mL/39.6–84 ng/mL	Human	6 h	-	[29–32]
		5 mg/kg	Intravenous	Thermal stimulus	Increase in thermal withdrawal threshold		-	-	-	-	[29–32]
Indian Peafowl	*Pavo Cristatus*	7.5 mg/kg	Oral	-	-	-	298–590 ng/mL/39.6–84 ng/mL	Human	Up to 2 h in 2 birds	12 h in 5/6 birds	[33]
Muscovy Duck	*Carina moschata*	30 mg/kg	Oral	Difference in maximum force between arthritis-induced and non-arthritis induced legs	Significant difference between both tramadol and meloxicam vs. control	Up to 4 h	298–590 ng/mL/39.6–84 ng/mL	Human	At least 12 h	At least 6 h	[7,34]

Table 3. *Cont.*

Species Name		Dosing Regimen		PD Study			Plasma Concentration				
English	Scientific	Dose	Administration	Type	Result	Duration	Target (Parent/Metabolite)	Source	Duration ≥ Target Concentration		Reference
									Opioid	Metabolite	
HYDROMORPHONE											
American Kestrel	*Falco sparverius*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Thermal stimulus	0.6 mg/kg—Significant increase in thermal foot withdrawal threshold	3 h	>1 ng/mL	American kestrel	0.6 mg/kg—3–6 h	-	[35,36]
Cockatiel	*Nymphicus hollandicus*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Thermal stimulus	Did not increase thermal foot withdrawal threshold	-	>1 ng/mL	American kestrel	0.6 mg/kg—3–6 h	-	[50]
Orange-winged Parrot	*Amazona amazonica*	0.1 mg/kg 1 mg/kg 2 mg/kg	Intramuscular	Thermal stimulus	Significant increase in thermal foot withdrawal threshold	When administered 1 mg/kg and 2 mg/kg—3 h and 6 h respectively	>1 ng/mL	American kestrel	1 mg/kg—6 h in 8/8 birds	-	[38,39]
		1 mg/kg	Intravenous	-[1]	-	-	>1 ng/mL	American kestrel	6 h; 6/7 birds	-	
BUPRENORPHINE											
Grey Parrot	*Psittacus erithacus*	0.1 mg/kg	Intramuscular	Electric stimulus	No significant change in electrical withdrawal threshold	-	>1 ng/mL	Human	2 h	-	[40,41]
		0.1 mg/kg	Intravenous	-	-	-	>1 ng/mL	Human	2 h	-	[40,41]
American Kestrel	*Falco sparverius*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Thermal stimulus	Significant increase in thermal foot withdrawal threshold	All doses tested—6 h	>1 ng/mL	Human	0.6 mg/kg–9 h [2]	-	[42,43]
		1.8 mg/kg	Subcutaneous (sustained-release)	-	-	-	> 1 ng/mL	Human	48 h	-	[44]
		1.8 mg/kg	Intramuscular (sustained-release)	Thermal stimulus	Significant increase in thermal foot withdrawal threshold	Up to 24 h	>1 ng/mL	Humans	48 h	-	[44,45]
		0.6 mg/kg	Intravenous	-	-	-	>1 ng/mL	Human	9 h	-	[43]

Table 3. *Cont.*

Species Name		Dosing Regimen		PD Study			Plasma Concentration				
English	Scientific	Dose	Administration	Type	Result	Duration	Target (Parent/Metabolite)	Source	Duration ≥ Target Concentration		Reference
									Opioid	Metabolite	
Red-tailed Hawk	*Buteo jamaicensis*	0.25 mg/kg	Intramuscular	-[3]	-	-	-	-	-	-	[46]
		0.3 mg/kg 1.8 mg/kg	Subcutaneous (concentrated)	-	-	-	>1 ng/mL	Human	0.3 mg/kg—24 h; 1.8 mg/kg—48 h	-	[47]
Cockatiel	*Nymphicus hollandicus*	0.6 mg/kg 1.2 mg/kg 1.8 mg/kg	Intramuscular	Thermal stimulus	No significant increase in thermal withdrawal threshold	-	> 1 ng/mL	Human	9 h; 4/4 birds	-	[48]
BUTORPHANOL											
Hispaniolan Parrot	*Amazona ventralis*	5 mg/kg	Oral	-	-	-	100 ng/mL	Hispaniolan amazon parrots	-	-	[49]
		2 mg/kg [4] 5 mg/kg	Intramuscular	-	-	-	100 ng/mL	Hispaniolan amazon parrots	-	-	[49,50]
		5 mg/kg	Intravenous	-	-	-	100 ng/mL	Hispaniolan amazon parrots	-	-	[49]
		10 mg/kg 15 mg/kg	Subcutaneous (Liposome-Encapsulated)	Electrical and thermal stimuli	Significant increased in electrical and thermal withdrawal threshold	Up to 5 days	-[5]	-	-	-	[50,52]
		12 mg/kg	Subcutaneous (Long-Acting)	-	-	-	100 ng/mL	Hispaniolan amazon parrots	>3 h (all birds) or >4 h (5/8 birds) but < 8 h (all birds)	-	[51]
Grey Parrot and Timneh Parrot	*Psittacus erithacus and Psittacus timneh*	1 mg/kg	Intramuscular	Electric stimulus-	Significant increase in electrical withdrawal threshold	-	-	-	-	-	[41]

Table 3. *Cont.*

Species Name		Dosing Regimen		PD Study			Plasma Concentration				
English	Scientific	Dose	Administration	Type	Result	Duration	Target (Parent/Metabolite)	Source	Duration ≥ Target Concentration		Reference
									Opioid	Metabolite	
Sulphur-crested Cockatoo and Yellow-crested Cockatoo	*Cacatua galerita, Cacatua sulphurea cintrinocristata and Cacatua sulphurea sulphurea*	1 mg/kg	Intramuscular	-	-	-	-	-	-	-	[16]
Red-tailed Hawk	*Buteo jamaicensis*	0.5 mg/kg	Intravenous	-	-	-	9–30 ng/mL	Dogs, horses & llamas [6]	2–4 h	-	[53]
		0.5 mg/kg	Intramuscular	-	-	-	9–30 ng/mL	Dogs, horses & llamas [7]	2–4 h	-	[53]
Great Horned Owl	*Bubo virginianus*	0.5 mg/kg	Intravenous	-	-	-	9–30 ng/mL	Dogs, horses & llamas [8]	2–4 h	-	[53]
		0.5 mg/kg	Intramuscular	-	-	-	9–30 ng/mL	Dogs, horses & llamas [9]	2–4 h	-	[53]
American Kestrel	*Falco sparverius*	1 mg/kg 3 mg/kg 6 mg/kg	Intramuscular	Thermal stimulus	Significantly increased in female compared with baseline but not significant compared with control	-	100 ng/mL	Humans	2 h	-	[54]
Broiler Chicken	-	2 mg/kg	Intravenous	-	-	-	55–70 ng/mL	Unknown	2 h	-	[55]
Indian Peafowl	*Pavo cristatus*	120 µg/kg/hr with rate 48.1 mg/mL [10]	Osmotic pump	-	-	-	60 µg/mL	Hispaniolan amazon parrots	85.6 h (mean)	-	[56]

Table 3. *Cont.*

Species Name		Dosing Regimen		PD Study			Plasma Concentration				
English	Scientific	Dose	Administration	Type	Result	Duration	Target (Parent/Metabolite)	Source	Duration ≥ Target Concentration		Reference
									Opioid	Metabolite	
FENTANYL											
Chickens (Brahma, Delaware, Redstar and Wyandotte)	-	25 µg/h for 30 s	Transdermal	-	-	-	0.2–1.2 ng/mL	Human	72 h	-	[59]
Helmeted Guineafowl	*Numida meleagris*	5 mg/kg	Transdermal	-	-	-	8.51–29.25 ng/mL	Dogs	At least 7 days	-	[58]
White Cockatoo	*Cacatua alba*	0.01 mg/kg 0.02 mg/kg	Intramuscular	Thermal and electrical stimuli	No increase in electrical and thermal withdrawal thresholds	-	0.2 ng/mL	Human	0.02 mg/kg—300 min	-	[57]
		0.1 mg/kg	Subcutaneous	Thermal and electrical stimuli	Significant increase in thermal and electrical withdrawal thresholds	-	0.2 ng/mL	Human	-	-	[57]

[1] Similar PK profile to that of IM hydromorphone. Efficacy can be assumed. [2] PK data in birds treated with 0.1 and 0.3 mg/kg buprenorphine are not available. [3] This study's main objective is not to evaluate antinociception nor study pharmacokinetics of buprenorphine but to evaluate behaviors associated with pain in red-tailed hawks. The study did not give direct evidence of analgesia after administration of buprenorphine to red-tailed hawks and buprenorphine did not return hawks with trauma to normal behavior. [4] This study shows butorphanol as an effective pre-emptive analgesia with sevoflurane anesthesia. [5] This study shows when butorphanol reach plasma concentration of 80 ng/mL, withdrawal thresholds to electrical and thermal stimuli were increased. [6] Based on study in dogs (9–10 ng/mL), horses (20–30 ng/mL) and llamas (9.2–23.8 ng/mL). [7] Based on study in dogs (9–10 ng/mL), horses (20–30 ng/mL) and llamas (9.2–23.8 ng/mL). [8] Based on study in dogs (9–10 ng/mL), horses (20–30 ng/mL) and llamas (9.2–23.8 ng/mL). [9] Based on study in dogs (9–10 ng/mL), horses (20–30 ng/mL) and llamas (9.2–23.8 ng/mL). 1^0 Infusion rate = target plasma butorphanol concentration ×Cl = 60 µg/L × 2 L/kg/h = 120 µg/kg/h. Required concentration = infusion rate × bird's body weight/temperature-adjusted pump rate = 120 µg/kg/h × 4.45 kg/11.1 µL/h = 48.1 µg/µL = 48.1 mg/mL.

4.1. Tramadol

The use of tramadol has been examined in several avian species including the Bald Eagle (*Haliaetus leucocephalus*) [24,25], American Kestrel (*Falco sparverius*) [26], Red-tailed Hawk (*Buteo jamaicensis*) [25,27], African Penguin (*Spheniscus demersus*) [28], Hispaniolan Amazon (*Amazona ventralis*) [29–32], Indian Peafowl (*Pavo cristatus*) [33] and Muscovy Duck (*Carina moschata*) [7,34]. Tramadol is a weak opioid agonist, which is highly specific to the μ-receptor, which also acts as a weak serotonin and norepinephrine reuptake inhibitor [60–62]. Tramadol has numerous metabolites [63], but only O-desmethyltramadol (M1), which is a result of the demethylation of tramadol in the liver, has been shown to have clinically important analgesic properties in human [64].

The mean therapeutic plasma concentrations of tramadol and O-desmethyltramadol associated with analgesia in humans are 298 ± 171 ng/mL to 590 ± 410 ng/mL and 39.6 ± 29.5 ng/mL to 84 ± 34 ng/mL, respectively [65,66]. Since the plasma therapeutic concentrations of tramadol and O-desmethyltramadol in avian species are unknown, efficacy is assumed if therapeutic plasma concentration of tramadol reached the plasma concentration associated with analgesia in human.

With this assumption, generally tramadol is effective in providing analgesia among the avian species studied. Target concentrations are reached among all species used in PK studies. The duration where plasma concentration reached or exceeded target concentration ranged from 2 h to at least 12 h. However, only studies involving Muscovy Duck [7,34], American Kestrel [26] and Hispaniolan Amazon [29–31] are supported by PD evidences. These PD studies showed effectiveness of oral tramadol 30 mg/kg, oral tramadol 5 mg/kg and oral tramadol 30 mg/kg in Muscovy Duck, American Kestrel and Hispaniolan Amazon, respectively, in providing an analgesic effect to thermal stimulus. In the study involving oral tramadol in American Kestrel, it is observed that a higher tramadol concentration i.e., 15 mg/kg and 30 mg/kg provided a shorter duration and increments in thermal threshold values of up to 3 h after administration compared with 9 h after administration of 5 mg/kg oral tramadol.

Separately, it was found in Hispaniolan Amazon that oral tramadol 10 mg/kg and 20 mg/kg did not significantly increase thermal foot withdrawal threshold, but oral tramadol 30 mg/kg significantly increased thermal foot withdrawal threshold for up to 6 h. At the same time, a PK study also showed that 30 mg/kg oral tramadol given to Hispaniolan Amazon reached the minimum plasma concentration considered analgesic in humans for up to 6 h. Since birds used for the 2 studies were from the same population, it can be assumed that results from the PK study can be applied to the PD study [31,32]. With that assumption, it could be deduced that the minimum effective plasma tramadol concentration of Hispaniolan Amazon is similar to humans.

Since birds do produce O-desmethyltramadol metabolites after the administration of tramadol, variability of analgesic effects of tramadol across different species may occur, depending on variability in biotransformation of tramadol in certain species [25]. However, given there is limited paired PK and PD studies to assess the efficacy of tramadol and there is no study assessing the analgesic effect of O-desmethyltramadol in birds, there is no consensus whether O-desmethyltramadol contributes to analgesic effect in avian species.

4.2. Hydromorphone

Hydromorphone, also known as dihydromorphinone, is a semi-synthetic μ-opioid receptor agonist, which also displays weak affinity for κ-opioid receptors [67]. The use of hydromorphone has been examined in several avian species including American Kestrel (*Falco sparverius*) [35,36], Cockatiel (*Nymphicus hollandicus*) [37] and Orange-winged Amazon (*Amazona amazonica*) [38,39].

Since therapeutic plasma concentrations of hydromorphone is unknown in avian species, dosing recommendations were selected based on PK and PD studies done on American Kestrel, which suggested a thermal antinociceptive effect at plasma concentration of >1 ng/mL [35,36].

Generally, plasma concentrations of all species studied reached or exceeded plasma concentrations associated with analgesia in American Kestrel, with duration ranging from 3 to 6 h. PD studies conducted in American Kestrel [35,36] and Orange-winged Amazon [38,39] showed the effectiveness of hydromorphone in providing an analgesic effect to thermal stimuli at the given plasma concentration. One exception, however, is that of cockatiel [37]. Despite reaching plasma concentrations associated with analgesia in American kestrel, there is no significant increase in the thermal withdrawal threshold in cockatiel receiving 0.6 mg/kg hydromorphone [37]. The reason for this is unclear, but this highlights potential difference in analgesia mechanisms between cockatiel as compared to American Kestrel. Furthermore, opioid interactions with μ-opioid receptors usually contributes to analgesic [68,69] and adverse effects of opioids such as respiratory depression, constipation, sedation, nausea, vomiting, euphoria and withdrawal [70]. However, despite the presence of mild sedation for cockatiels receiving 0.3 mg/kg and 0.6 mg/kg IM hydromorphone, the thermal withdrawal threshold did not increase significantly [37]. This further emphasizes potential differences between the mechanisms that contribute to analgesic effects and adverse effects in cockatiels, as compared to other species of birds studied.

4.3. Buprenorphine

Buprenorphine is believed to be a mixed agonist/antagonist. It was reported that its analgesic action is largely from its μ-opioid receptor agonism [71], but studies in rats and mice have shown buprenorphine antagonist action against μ-opioid receptors [72]. Its action on κ-opioid receptor also remains inconclusive [73–75]. Although the exact mechanism of its analgesic effect still remains uncertain [4], buprenorphine is shown to be an effective analgesic agent in animals [76].

Buprenorphine exhibits ceiling analgesic effect [77–80]. It binds strongly to opiate receptors, dissociates slowly from the receptors and it has a long-acting analgesic effect in mammalian species [79,81]. Plasma buprenorphine concentration may decline rapidly but its analgesic effect may remain, likely because of its strong binding to opiate receptors and slow dissociation from the receptors. Therefore, the relationship between plasma concentration and its analgesic effect may not be direct [79].

In humans, the plasma concentration of buprenorphine associated with analgesia is >1-ng/mL [82]. Hence, the efficacy of buprenorphine in providing analgesic effect is generally assumed when the plasma concentration of buprenorphine in birds reaches > 1 ng/mL.

Use of buprenorphine in avian species have been examined in Grey Parrot (*Psittacus errithacus*) [40,41], American Kestrel (Falco sparverius) [42,43], Red-tailed hawk (*Buteo jamaicensis*) [46], Rock Dove (*Columba livia*) [83] and Cockatiel (*Nymphicus hollandicus*) [48].

Generally, plasma concentrations of buprenorphine in bird species studied reached or exceeded buprenorphine plasma concentration associated with analgesia in human (1 ng/mL). PD studies done also showed an increase in thermal withdrawal threshold in American Kestrel treated with buprenorphine. However, a separate PD study involving Grey Parrot [40,41] and Cockatiel [48] showed no significant increase in electrical and thermal withdrawal thresholds at the doses given. A PK study performed on cockatiels did not observe analgesic effect even though the plasma concentration of buprenorphine reached target concentration for 9 h.

In addition, the mean withdrawal threshold in male American Kestrel was significantly higher than female American Kestrel, highlighting a potential difference attributable to sex [42,43].

4.4. Butorphanol

Butorphanol is a synthetic, mixed agonist/antagonist at the μ-opioid receptors. It is also a partial agonist at the κ-opioid receptors, which is present at a higher proportion in birds as compared to other species [84]. The affinity of butorphanol is reported to be stronger to κ-opioid receptors as compared to μ-opioid receptors [85,86].

The target plasma concentration associated with analgesia in articles collated are different for each study. These target concentrations are reflected in Table 3.

Butorphanol has been studied in Grey Parrot and Timneh Parrot (*Psittacus erithacus* and *Psittacus timneh*) [41], Red-tailed Hawk (*Buteo jamaicensis*) [53], Great Horned Owl (*Bubo virginianus*) [53], Hispaniolan Amazon (*Amazona ventralis*) [49–51], Broiler Chicken [55], Indian Peafowl (*Pavo cristatus*) [56], Sulphur-crested Cockatoo and Yellow-crested Cockatoo (*Cacatua galerita*, *Cacatua sulphurea cintrinocristata* and *Cacatua sulphurea sulphurea*) [16] and American Kestrel (*Falco sparverius*) [54].

Generally, the use of butorphanol is likely to be effective in all species studied as various PK studies saw the plasma concentration of butorphanol reaching or exceeding target plasma concentration in the species studied. PD studies had also shown significant increase in thermal or electric withdrawal stimuli, except for male American Kestrel. Interestingly, hyperalgesia or hyperesthesia were observed at 1.5 h (Cmax) in male Kestrels administered 6 mg/kg butorphanol [54]. This is a sex dependent response between male and female American Kestrel, whereby thermal withdrawal thresholds, when compared with baseline value, were significantly decreased in male compared to significantly increased in female. The reason for this is unclear.

4.5. Fentanyl

Fentanyl is a synthetic, short-acting opiate, which produces its analgesic effect through μ-opioid receptor agonism [87]. The use of fentanyl have been studied in Helmeted Guineafowl (*Numida meleagris*) [58], chicken [44,45] and White Cockatoo (*Cacatua alba*) [57].

Generally, the plasma concentration of all species studied reached or exceeded target concentration. PD studies to evaluate the effectiveness of fentanyl in producing analgesic effect to thermal and electrical stimuli were studied only in White cockatoo. Despite plasma concentration of White Cockatoo reaching plasma concentration associated with analgesia in humans when administered 0.01 mg/kg and 0.02 mg/kg of fentanyl, there was no significant increase in withdrawal threshold to electrical and thermal stimuli. However, significant increase in thermal and electrical withdrawal threshold were noticed when 10-fold increase in dose (0.2 mg/kg) were administered. It appears that White Cockatoo might need higher plasma concentrations of fentanyl to provide analgesia, as compared to human, which further emphasize differences between species that may lead to different outcomes.

4.6. Special Formulations of Opioids Impacting Efficacy of Opioids

Other than standard formulations, special formulations of buprenorphine and butorphanol were also studied in avian species. Concentrated and sustained-release formulation of buprenorphine were studied in Red-tailed Hawk [47] and American Kestrel [44,45], respectively. Long-acting (LA) poloxamer 407 gel formulation [51] butorphanol and liposome-encapsulated butorphanol (LEBT) [50,52] were studied in Hispaniolan Amazon.

4.6.1. Buprenorphine

Both the concentrated formulation of buprenorphine and sustained-release buprenorphine provided longer duration where plasma concentrations of buprenorphine were at or above the target concentration, implying longer duration of effectiveness in providing analgesic effect. In red-tailed hawk, administration of 0.3 mg/kg and 1.8 mg/kg concentrated buprenorphine resulted in a duration where plasma concentration of buprenorphine reached or exceeded target concentration for 24 h and 48 h, respectively. In addition, administration of 1.8 mg/kg sustained-release buprenorphine SC and IM to American Kestrel resulted in duration where plasma concentration of buprenorphine reached or exceeded target concentration for 48 h. These durations are longer than that of standard formulation studied in other bird species, whereby duration where plasma concentration reached or exceeded target concentration ranged from 2–9 h. Therefore, these formulations of buprenorphine could be used clinically if longer duration of action is desired.

4.6.2. Butorphanol

Liposome-encapsulated butorphanol was studied in Hispaniolan Amazon. However, the duration where plasma concentration of butorphanol was at or beyond target concentration was not reported and hence its ability to provide longer analgesic effect is still unclear. On the other hand, LA butorphanol produced plasma concentrations at or beyond target concentration for up to 4–8 h, which is longer than that of other formulation studied, where range of duration were typically only up to 4 h. Hence, LA butorphanol could be used clinically, if deemed necessary.

5. Trends in Efficacy of Selected Opioids

Generally, at the doses given, plasma concentration of opioids among most bird species reached or exceeded target concentration. Furthermore, analgesic effects were observed among species studied.

Interestingly, Cockatiel did not seem to benefit from analgesic effect of μ-receptor agonists, hydromorphone and buprenorphine, despite reaching target plasma concentration. The reason for this is unclear. However, a study comparing expressions of opioid receptors between Cockatiel and Rock Dove showed that Cockatiel has less μ-opioid receptor expressions in the footpad as compared to Rock Dove [88]. This may explain the reason for non-significant increase in thermal or electrical withdrawal threshold in cockatiels despite presence of adverse effects associated with interactions with μ-receptor. However, further studies need to be done to assess this.

Another observation point is the sex-dependent response between male and female American Kestrel after administration of buprenorphine and butorphanol. Although the exact reason is unclear, it is noted that American Kestrel exhibit sexual dimorphism, whereby female American Kestrel are generally larger and heavier than male Amarican Kestrel [89]. Weight may affect PK in terms of absorption or distribution, which may explain difference in responses between male and female American Kestrel. However, this may not be true as the use of tramadol and hydromorphone in American Kestrel did not produce significant sex-dependent response. Further studies need to be conducted to investigate the sex-dependent response.

Special formulations of buprenorphine and butorphanol were studied and resulted in longer duration where plasma concentration was reached or exceeded target concentration, implying longer duration of analgesic effect in the species studied. These formulations could be used clinically if longer duration of analgesic effect is deemed necessary.

6. Evaluation of Dosing Regimens in Relation to Safety Evidence

Table 4 shows the adverse effects of selected opioids used in particular species of birds. The use of opioids appeared to be safe for avian species, with the most common adverse effect being sedation. There was no severe adverse event such as death observed with the use of these opioids, although there were a few moderate adverse events such as ataxia, apnea, miosis, vomiting and bradycardia that was not clinically significant. It was also observed, from studies administering more than 1 dosing regimen of a specific opioids to a particular species of birds, that adverse events were generally dose-dependent. Gastrointestinal (GI) adverse effects of tramadol were observed in American Kestrels only when they were administered 15 mg/kg and 30 mg/kg tramadol, but this adverse effect was not observed when kestrels were given 5 mg/kg tramadol.

Table 4. Adverse effects of selected opioids reported in species studied.

Species Name		Dosing Regimen		Adverse Effect	Reference
English	**Scientific**	**Dose**	**Administration**		
			TRAMADOL		
Bald Eagle	*Haliaeetus leucocephalus*	11 mg/kg	Oral	None observed	[24,25]
		4 mg/kg	Intravenous	Mild transient bradycardia observed immediately after administration until 10 min after IV administration in 3 birds. Bradycardia is deemed clinically insignificant.	
American Kestrel	*Falco sparverius*	5 mg/kg 15 mg/kg 30 mg/kg	Oral	GI adverse effect observed at higher doses (15 mg/kg and 30 mg/kg). Vomiting observed in 1 kestrel within 30 min after administration of tramadol 30 mg/kg. Polyuria observed for 6 birds—1 control; 2 treated with 15 mg/kg tramadol; 3 treated with 30 mg/kg	[26]
Red-tailed Hawk	*Buteo jamaicensis*	11 mg/kg	Oral	None observed	[25,27]
Jackass Penguin	*Spheniscus Demersus*	10 mg/kg	Oral	Penguins were subjectively quieter 1–1.5 h post administration & considered back to normal after 6 h of administration. This could be due to frequent handling. Monitor for signs of sedation.	[28]
Hispaniolan Parrot	*Amazona ventralis*	30 mg/kg	Oral	No sedation or changes in behavior were detected. Birds had ruffled feathers and were quiet after handling but did not have other signs of stress.	[29–32]
		5 mg/kg	Intravenous		[29–32]
Indian Peafowl	*Pavo Cristatus*	7.5 mg/kg	Oral	No adverse effects or changes in behavior noted	[33]
Muscovy Duck	*Carina moschata*	30 mg/kg	Oral	No adverse effects noted	[7,34]
			HYDROMORPHONE		
American Kestrel	*Falco sparverius*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Appreciable sedation detected in 4 birds after administration of 6 mg/kg hydromorphone	[35,36]
Cockatiel	*Nymphicus hollandicus*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Sedation after administration of 0.3 mg/kg and 0.6 mg/kg hydromorphone	[50]
Orange-winged Parrot	*Amazona amazonica*	0.1 mg/kg 1 mg/kg 2 mg/kg	Intramuscular	Treatment was significantly ($p < 0.001$) associated with nausea-like behavior. Other adverse effect includes ataxia and miosis.	[38,39]
		1 mg/kg	Intravenous	Not reported	
			BUPRENORPHINE		
Grey Parrot	*Psittacus erithacus*	0.1 mg/kg	Intramuscular	Not reported	[40,41]
		0.1 mg/kg	Intravenous		

Table 4. *Cont.*

Species Name		Dosing Regimen		Adverse Effect	Reference
English	**Scientific**	**Dose**	**Administration**		
American Kestrel	*Falco sparverius*	0.1 mg/kg 0.3 mg/kg 0.6 mg/kg	Intramuscular	Mild to moderate sedation was recorded within 15 to 30 min after both IM and IV administration of 0.6 mg of buprenorphine/kg, although the birds remained reactive to physical handling at all time points.	[42,43]
		0.6 mg/kg	Intravenous		[43]
		1.8 mg/kg	Subcutaneous (sustained-release)	There was no subjectively appreciable sedation after either IM or SC administration.-	[44]
		1.8 mg/kg	Intramuscular (sustained-release)		[44,45]
Red-tailed Hawk	*Buteo jamaicensis*	0.25 mg/kg	Intramuscular	-[1]	[46]
		0.3 mg/kg 1.8 mg/kg	Subcutaneous (concentrated)	Mean agitation-sedation scores were higher (indicating some degree of sedation) than the baseline values for 24 h at both doses. No clinically important adverse effects were observed.	[47]
Cockatiel	*Nymphicus hollandicus*	0.6 mg/kg 1.2 mg/kg 1.8 mg/kg	Intramuscular	Did not significantly cause sedative or agitative effects	[48]
			BUTORPHANOL		
Hispaniolan Parrot	*Amazona ventralis*	5 mg/kg	Oral	Significant adverse effects were not observed	[49]
		2 mg/kg [2] 5 mg/kg	Intramuscular	Significant adverse effects were not observed	[49,50]
		5 mg/kg	Intravenous	Significant adverse effects were not observed but 1 parrot developed apnea for a short period.	[49]
		10 mg/kg 15 mg/kg	Subcutaneous (Liposome-Encapsulated)	No observable adverse effect although there were mild-moderate sedation between 1–2 h after administration.	[50,52]
		12 mg/kg	Subcutaneous (Long-Acting)	All birds were subjectively quieter after administration of butorphanol. Furthermore, 2 birds receiving 16.6 mg/kg SC vomited around 1.31 h post administration.	[51]
Grey Parrot and Timneh Parrot	*Psittacus erithacus and Psittacus timneh*	1 mg/kg	Intramuscular	Not reported	[41]
Sulphur-crested Cockatoo and Yellow-crested Cockatoo	*Cacatua galerita, Cacatua sulphurea cintrinocristata and Cacatua sulphurea sulphurea*	1 mg/kg	Intramuscular	Not reported	[16]
Red-tailed Hawk	*Buteo jamaicensis*	0.5 mg/kg	Intravenous	Mild sedation but no significant change in heart and respiratory rates	[53]
		0.5 mg/kg	Intramuscular		[53]
Great Horned Owl	*Bubo virginianus*	0.5 mg/kg	Intravenous	Mild sedation but no significant change in heart and respiratory rates	[53]
		0.5 mg/kg	Intramuscular		[53]

Table 4. *Cont.*

Species Name		Dosing Regimen		Adverse Effect	Reference
English	**Scientific**	**Dose**	**Administration**		
American Kestrel	*Falco sparverius*	1 mg/kg 3 mg/kg 6 mg/kg	Intramuscular	No sedative effect observed but male kestrels appeared agitated at 1.5 h.	[54]
Broiler Chicken	-	2 mg/kg	Intravenous	Not reported	[55]
Indian Peafowl	*Pavo cristatus*	120 µg/kg/h with rate 48.1 mg/mL [3]	Osmotic pump	No evidence of sedation or other adverse effect	[56]
		FENTANYL			
Chickens (Brahma, Delaware, Redstar and Wyandotte)	-	25 µg/h for 30 s	Transdermal	No adverse effects noted	[59]
Helmeted Guineafowl	*Numida meleagris*	5 mg/kg	Transdermal	No adverse effects noted	[58]
White Cockatoo	*Cacatua alba*	0.01 mg/kg 0.02 mg/kg	Intramuscular	None observed	[57]
		0.1 mg/kg	Subcutaneous	2/7 birds sedate at 20 min, 6 birds hyperactive between 20 and 60 min	[57]

[1] This study's main objective is not to evaluate antinociception nor study pharmacokinetics of buprenorphine but to evaluate behaviors associated with pain in red-tailed hawks. The study did not give direct evidence of analgesia after administration of buprenorphine to Red-tailed Hawks and buprenorphine did not return hawks with trauma to normal behavior. 2 This study shows butorphanol as an effective pre-emptive analgesia with sevoflurane anesthesia. [3] Infusion rate = target plasma butorphanol concentration ×Cl = 60 µg/L × 2 L/kg/h = 120 µg/kg/h. Required concentration = infusion rate × bird's body weight/temperature-adjusted pump rate = 120 µg/ kg/h × 4.45 kg/11.1 µL/h = 48.1 µg/µL = 48.1 mg/mL.

Another observation was the sex-dependent adverse effect in American Kestrels after the administration of butorphanol [54]. In this case, sedative effect was not observed but male Kestrels seemed to be agitated at 1.5 h post-administration. This observation was aligned with the observed sex-dependent response of efficacy in American Kestrels administered butorphanol.

7. Pharmacokinetics Variability

Table 5 shows the reported half-lives of selected opioids and their metabolites (if applicable) in various avian species studied.

Table 5. The reported half-lives of selected opioids in avian species studied.

Species		Weight	Dosage Studied	Route of Administration	Fed or Fasted	Formulation	C_{max} (ng/mL)	Bioavailability (%)	Half-Life (hr)		Reference
English	**Scientific**								**Parent Drug**	**Metabolite**	
TRAMADOL											
Bald Eagle	*Haliaeetus leucocephalus*	2.95–5.91 kg	11 mg/kg	Oral	Fasted 12 h before dosing	Suspension	2156.7 ± 681.4	97.9	3.14 ± 0.94	6.28 ± 1.72	[24,25]
		2.95–5.91 kg	4 mg/kg	Intravenous		-	-	-	2.46 ± 0.65	-	
Red-tailed Hawk	*Buteo jamaicensis*	Not reported	11 mg/kg	Oral	Fasted 12 h before dosing	Suspension	1412.3 ± 79.6	-	1.3 ± 0.6	1.9 ± 0.2	[25,27]
Jackass Penguin	*Spheniscus Demersus*	≥2.7 kg	10 mg/kg	Oral	Tramadol given with a fish. No additional fish offered untl 4 h later.	Capsules	-	-	7.3 ± 1.5	13.58 ± 4.38	[28]
Hispaniolan Parrot	*Amazona ventralis*	319 ± 30 g	30 mg/kg	Oral	Food withheld 2 h after administration	Suspension	1.67 ± 1.17	23.48 ± 6.96	4.85 ± 0.33	2.7 ± 0.38	[29–32]
		321 ± 28 g	30 mg/kg	Oral (BD, 5 days)	Food was not withheld	Suspension	409 ± 132	-	2.92 ± 0.78	2.14 ± 2.10	
		319 ± 30 g	5 mg/kg	Intravenous	Food withheld 2 h after administration	-	-		1.54 ± 0.51	2.55 ± 0.85	
Indian Peafowl	*Pavo Cristatus*	4.1 ± 0.4 kg	7.5 mg/kg	Oral	Not fasted. Free access to food.	Suspension	116.0 ± 79.14	-	1.68 ± 0.41	5.10 ± 2.29	[33]
Muscovy Duck	*Carina moschata*	2.6 ± 0.7 kg	30 mg/kg	Oral	Food withheld 2 h before procedure	Suspension	780 ± 300	-	3.95 ± 0.60	1.51 ± 1.21	[7,34]
HYDROMORPHONE											
Orange-winged Parrot	*Amazona amazonica*	402.6 ± 42 g	1 mg/kg	IM	Ad libitum access to water and pelleted diet	-	179.1 ± 28.4	97.6 ± 61.1	1.74 ± 0.351	-	[38,39,87]
		402.6 ± 42 g	1 mg/kg	Intravenous		-	-	-	1.45 ± 0.270	-	
American Kestrel	*Falco sparverius*	115 ± 6.2 g	0.6 mg/kg	IM	No access to food or water throughout blood sample collection	-	112.10	75	1.25	-	[35,36]
		115 ± 6.2 g	0.6 mg/kg	Intravenous		-	-	-	1.26	-	
Cockatiel	*Nymphicus hollandicus*	78.5–130.8 g	0.6 mg/kg	IM	Ad libitum access to water and pelleted diet	-	135.8	-	0.99	-	[37]
BUPRENORPHINE											
Grey Parrot	*Psittacus erithacus*	300–500 g	0.1 mg/kg	IM	-	-	68.7	-	1.04 ± 0.14	-	[40,41]
		300–500 g	0.1 mg/kg	Intravenous		-	-	-	1.04	-	
American Kestrel	*Falco sparverius*	Not reported	0.6 mg/kg	IM	Kestrels were fed killed, previously frozen mice or day-old chicks and had ad libitum access to water	-	242.9	94.9	1.54	-	[42–46]
		Not reported	0.6 mg/kg	Intravenous		-	-	-	1.76	-	
		Not reported	1.8 mg/kg	IM		Sustained release	69.2	-	11.1	-	
		Not reported	1.8 mg/kg	SC		Sustained release	72.3	-	13.5	-	
Red-tailed Hawk	*Buteo jamaicensis*	1.28 kg	0.3 mg/kg	SC	Food withheld 12 h prior to administration and normal feeding schedule resume 24 h after administration	Concentrated	74.1 ± 37.0	-	6.23 ± 0.31	-	[46,47]
		1.28 kg	1.8 mg/kg	SC		Concentrated	322.1 ± 57.7	-	7.84 ± 3.29	-	
Cockatiel	*Nymphicus hollandicus*	106 ± 19.6 g	0.6 mg/kg	IM	-	-	240 ± 44.3	-	2.31	-	[48]

Table 5. *Cont.*

Species		Weight	Dosage Studied	Route of Administration	Fed or Fasted	Formulation	C_{max} (ng/mL)	Bioavailability (%)	Half-Life (hr)		Reference
English	Scientific								Parent Drug	Metabolite	
BUTORPHANOL											
Hispaniolan Parrot	*Amazona ventralis*	289 g	5 mg/kg	Oral	Fed a commercially available pelleted diet ad libitum and had constant access to water	-	-	5.90	-	-	[49–52]
		289 g	5 mg/kg	IM		-	653.42	130	0.51	-	
		289 g	5 mg/kg	Intravenous		-	-	-	0.49	-	
		305.5 ± 18 g	12.5 mg/kg	SC		Long-acting poloxamer gel	452.3 ± 78.0	-	3.41 ± 3.44	-	
Great Horned Owl	*Bubo virginianus*	940 to 1450 g	0.5 mg/kg	Intravenous to right jugular vein	-	-	-	-	1.79 ± 1.36	-	[53]
		940 to 1450 g	0.5 mg/kg	Intravenous tp pectoral muscle	-		-		1.19 ± 0.34	-	
		940 to 1450 g	0.5 mg/kg	Intramuscular	-	-	229.9 ± 109.7	-	1.84 ± 1.56	-	
Red-tailed Hawk	*Buteo jamaicensis*	940 to 1450 g	0.5 mg/kg	Intravenous to right jugular vein	-	-	-	-	0.94 ± 0.30	-	[53]
		940 to 1450 g	0.5 mg/kg	Intramuscular	-	-	154.4 ± 70.0	-	0.94 ± 0.26	-	
Broiler Chicken	-	2 kg	2 mg/kg	Intravenous	They were fed ad libitum with commercial broiler feed and had access to fresh clean water.	-	-	-	1.16	-	[55]
American Kestrel	*Falco sparverius*	108.4 ± 6.4 g	6 mg/kg	Intramuscular	They were fed frozen-thawed, medium-sized mice and provided water ad libitum	-	445		1.48	-	[54]
FENTANYL											
Chickens (Delaware, Redstar and Wyandotte)	-	2.20–3.46 kg	25 µg/h for 30 s	Transdermal	Birds were fed routine diet, including daily free-choice of grain, varied seasonal produce, and water.	-	2.86 ± 2.58	-	7.1 ± 4.9	-	[59]
Chickens (Brahma and Wyandotte)	-	2.20–3.46 kg	25 µg/h for 30 s	Transdermal		-	2.86 ± 2.58	-	7.2 ± 3.7	-	[59]
Helmeted Guineafowl	*Numida meleagris*	1.38–1.94 kg	5 mg/kg	Transdermal	Birds had ad libitum access to water and exotic gamebird maintenance.	Solution	228.8	-	33.2	-	[58]
White Cockatoo	*Cacatua alba*	572 ± 125 g	0.01	Intramuscular	Water and a pelleted diet were proviccded ad libitum	-	2.23 ± 0.51	-	1.44 ± 0.45	-	[57]
		572 ± 125 g	0.02	Intramuscular		-	3.33 ± 1.06	-	1.16 ± 0.42	-	

7.1. Half-Life

7.1.1. Tramadol

As compared to that of other species, tramadol's half-life is longest in African Penguin (7.3 ± 1.5 h). M1's half-life is also longest in African Penguin (13.58 ± 4.38 h) [28] although the weight of African Penguin in this study was comparable to other species. The reason for this is unknown although tramadol was administered with food in this study as compared to the other study design where food was not administered, although unrestricted. Presence of food usually increases transit time, which increases time for absorption. However, assuming linear PK, since half-life is generally affected by volume of distribution and clearance, presence of food is unlikely the reason for tramadol's long half-life in African Penguin.

Generally, Red-tailed Hawk and Hispaniolan Amazon have the shortest half-lives of around 1.3 to 1.5 h [25,27,29–32]. Hispaniolan Amazon have the lowest weight among other species, which may explain its short half-life as weight may affect the volume of distribution and body size is correlated to basal metabolic rate. However, the reason for the shorter half-life of tramadol in red-tailed hawks is not clear.

In addition, the half-lives of tramadol in Hispaniolan Amazon were not consistent across the different routes of administration [29–32]. Its PO half-lives are higher than that of IV but it could be due to 6 times higher dose in PO as compared to IV. Conceptually, assuming linear PK, half-lives should be the same regardless of routes of administration and dose. This result may suggest tramadol, when administered to Hispaniolan Amazon, potentially exhibit saturable kinetics at higher doses. However, further study needs to be done to explain this observation.

7.1.2. Hydromorphone

The half-lives of hydromorphone in species studied range from 0.99–1.74 h, with the longest half-life in Orange-winged Amazon and shortest half-life in Cockatiel [38,39,50]. This could be explained by their weights as cockatiel are the lightest whereas Orange-winged Amazon are the heaviest.

7.1.3. Buprenorphine

Generally, the half-lives of buprenorphine in species administered with standard buprenorphine formulation range from 1.04–2.31 h, with Cockatiel having the longest half-life among other species [48]. In this case, cockatiel are lighter than Grey Parrot, but have a longer-half life as compared to Grey Parrot [40,41]. This observation shows weight may not always be the basis of drug extrapolation, even among the same order of avian species.

7.1.4. Butorphanol

The half-lives of butorphanol differ between species studied. It ranges from 0.49–1.79 h. Hispaniolan Amazon have the shortest half-life [49–52], which could be explained by its lightest weight. The Great Horned Owl appeared to have longer half-life than Red-tailed Hawk [53], which may be due to the presence of crops in Great Horned Owl that may withheld drug in the crop for a longer time.

7.1.5. Fentanyl

The half-lives of fentanyl in studied species range from 1.16–33.2 h. Helmeted Guineafowl have the longest half-life, which may be due to the long administration time of 7 days [58]. Other than that, there seems to be positive correlation between body weight and half-life, although no conclusion could be drawn yet given small number of species involved.

7.2. Bioavailability

In general, the bioavailability of opioids was not reported in most studies. From the available data, it was observed that the bioavailability of opioids were generally high at around 75% or more, except that of Hispaniolan Amazon, where the oral bioavailability of tramadol and butorphanol were only 23.48% and 5.90%, respectively [29–32,49–52].

For tramadol, among the species studied, Hispaniolan Amazon required a dose of 30 mg/kg to reach or exceed target plasma tramadol concentration in humans for up to 6 h. This dose is generally higher than other species studied which could be due to lower tramadol bioavailability of 23.48% in parrots, as compared with 97.94% in eagles that only required 11 mg/kg oral tramadol to achieve the minimum effective tramadol concentration for up to 10 h. A similar observation was made for butorphanol, where the bioavailability of oral butorphanol in Hispaniolan Amazon was only 5.90%. The reason for this is unclear. Since there are no other studies available involving the use of oral butorphanol in other avian species, it is difficult to deduce whether Hispaniolan Amazon, as compared to other avian species, generally have low bioavailability for oral formulation of selected opioids, or bioavailability of butorphanol is generally low. In human, the bioavailability of oral butorphanol is very low (5%) as it undergoes extensive first-pass metabolism [90]. Therefore, this could also possibly be the reason for the low oral bioavailability of butorphanol in birds.

Further research and study can be performed to assess the bioavailability of oral drugs in Hispaniolan Amazon compared to other bird species to explore bioavailability trend that may help advise oral dosing regimens in Hispaniolan Amazon.

8. Conclusions

This critical review found specific dosing regimens of tramadol for Indian peafowl, Muscovy Duck, and Hispaniolan Amazon [25,27,29–32]; hydromorphone for Orange-winged Amazon [38]; buprenorphine for Cockatiel, American Kestrel and Grey Parrot [40,41,48]; and butorphanol for Hispaniolan Amazon, Broiler Chicken and Indian Peafowl [49–52] which were not reported in the EAF. These regimens, if found to be effective based on the related PK and PD studies, could be used in practice.

In terms of efficacy, cockatiel did not seem to benefit from the analgesic effect of hydromorphone [50] and buprenorphine [48]. Furthermore, American Kestrel appeared to exhibit sex-dependent response to opioids [42–46]. More studies have to be performed to elucidate the reasons for these observations.

The use of these opioids were generally safe, with sedation being the most common adverse effect reported. Moderate adverse effects such as nausea-like behavior and GI adverse effects have been reported but no severe adverse effect such as death was seen. When using these opioids, one should monitor for these adverse effects, which are generally dose-dependent.

In terms of PK, an interesting observation was the lower bioavailability of oral tramadol in Hispaniolan Amazon compared to the bald eagle [29–32,49–52]. Additionally, low bioavailability of butorphanol was also observed in Hispaniolan Amazon. This could be due to the nature of butorphanol which has very low bioavailability in humans. Further research should be conducted to draw a firm conclusion on the oral bioavailability of drugs in Hispaniolan Amazon.

The main limitation of our work was that a systematic review approach was not undertaken. (Appendix B shows the items that this study fulfilled from the PRISMA checklist for systematic review). Hence, it may be possible that additional evidence of the PD and PK effects of the selected opioids may have been missed. Also, only publications in English were included. Our review highlights an urgent need for mechanistic studies to be performed to understand the underlying reasons for the variabilities observed. Coupled with more PD and PK studies in various avian species, a larger body of data may unveil any PD or PK trends that could then guide more accurate dose extrapolation to other bird species.

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Appendix A

Table A1. Keywords used in search strategy.

Concept	Keywords
Opioids	Opioid, Opioids, Morphine, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Levorphanol, Meperidine, Tramadol, Methadone, Fentanyl, Hydromorphone, Tapentadol, Oxymorphone, Oxycodone
Bird	Bird, Birds, Aves, Avian
Pharmacokinetics and Pharmacodynamics	PK or Pharmacokinetic or Pharmacokinetics or Disposition or Absorption or Absorbed or Bioavailability or Biological Availability or AUC or Area Under the Curve or Area-under-curve or Half life or Half-life or Distribution or Distributed or Volume of distribution or Metabolism or Metabolised or Metabolized or Biotransformation or Metabolic Activation or Metabolic Inactivation or Excretion or Elimination or Clearance or Dosing or Dosage or Dosage Regimen or Dosage Regimens or Therapeutic concentration or Therapeutic concentrations or Therapeutic drug concentration or Therapeutic drug concentrations or PD or Pharmacodynamics or Pharmacodynamic or Analgesia or Analgesic or Analgesics or Analgesic activity or Analgesic activities

Appendix B

Table A2. PRISMA checklist.

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
TITLE			
Title	1	Identify the report as a systematic review.	NA because it is a critical, not systematic, review
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract Line 21–35
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction Line 39–102
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 106–108

Table A2. *Cont.*

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Method section (line 109–119). Did not include exclusion criteria.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Method section line 110
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Search term in Appendix A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	The first author collected the data
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Method section line 116–119
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Conversion of units for some of the data

Table A2. *Cont.*

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	NA
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA

Table A2. *Cont.*

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Sections 3–7
	23b	Discuss any limitations of the evidence included in the review.	NA
	23c	Discuss any limitations of the review processes used.	Line 434–436
	23d	Discuss implications of the results for practice, policy, and future research.	Section 8 Conclusion
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Under Funding statement
Competing interests	26	Declare any competing interests of review authors.	Under conflict of interest declaration
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	All data presented in the table can be found in the references cited

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