Comparison of efficacy of topical diclofenac sodium 1% gel and oral acetaminophen extended- or sustained-release for treatment of symptomatic knee osteoarthritis.

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Background

- Osteoarthritis (OA) is the most common form of arthritis, affecting over 32.5 million adults in the US[1]. OA is a degenerative joint disease characterized by break down of the cartilage and changes to the bone which slowly worsen over time. Symptoms of OA include joint pain, stiffness and swelling which can lead to reduced function and productivity.[1]
- There is no cure for OA, however symptoms can be managed by pharmacological and non-pharmacological therapies, including over-the-counter (OTC) medications.
- Two of the most-commonly recommended OTC options to treat OA symptoms are the topical non-steroidal anti-inflammatory drug (NSAID) diclofenac sodium gel (DSG) 1% and oral acetaminophen. Current American College of Rheumatology (ACR) OA guidelines[2] strongly recommend topical NSAIDs as front-line treatment for Knee OA symptoms and conditionally recommends acetaminophen. The current Osteoarthritis Research Society International (OARSI) OA guidelines[3] also strongly recommends topical NSAIDs for knee OA with no recommendation for acetaminophen.

Objectives

- The purpose of this review is to compare the published clinical efficacy data of DSG to that of acetaminophen extended-release (AER) and acetaminophen sustained-release (ASR) for treatment of knee OA symptoms.

Methods

Study design:

Retrospective evaluation of published placebo-controlled trials that used the Western Ontario and McMasters Osteoarthritis Index (WOMAC)[4] to examine the efficacy of DSG 1% to AER or ASR in the treatment of knee OA.

Literature search:

A literature search through February 2023 (PubMed and EMBASE) screened for placebo-controlled clinical studies that used the Western Ontario and McMaster Osteoarthritis Index (WOMAC) to evaluate treatment of symptomatic knee OA with either DSG or AER/ASR. Five 12-week studies were included in this review:

- Two studies evaluating DSG 1% (4g applied to 1-2 knees QID)[5,6]
- Two studies evaluating AER (1300 mg, TID)[7,8]
- One study evaluating ASR (2000 mg, BID) and AER (1300 mg, TID)[9]

Study endpoints:

% reduction from baseline in WOMAC subscale scores at 12 weeks:

- WOMAC pain
- WOMAC physical function
- WOMAC stiffness

Based on prior unpublished data, one DSG 1% study[5,10] included a Modified Efficacy Subpopulation (MES) which was defined after study completion, but prior to unblinding, which excluded:

- Patients who reported a decrease in Pain on Movement in the target knee between screening and baseline visit
- Patients with a score of ≥ 2 (out of 8) on an abridged WOMAC pain index for the contralateral knee at baseline

Results

Patient demographics and characteristics

- A total of 5 studies were included in the analysis:
  - DSG 1% (2 studies)
  - AER (2 studies)
  - ASR (1 study)
- Patient demographics and characteristics (Table 1)
  - ≤ 37% male, ≥ 63% female
  - Mean age for each treatment group between 59.2 and 63.1 years
- Patients had knee OA with baseline mild-moderate or moderate-severe pain in target joint
  - OA in 1[5] or 1-2[6] knees
  - OA in the knee (80-90%) or hip (10-20%)[7-9]
  - Kellgren-Lawrence Grading in target joint between
    - Grade 1-Grade 3[5,6]
    - Grade 2-Grade 3[7]
    - Grade 2-Grade 4[9]

Table 1. Demographics and Key Characteristics of Study Populations.

Study	Treatment groups (N)	Gender M/F (%)	Age, Mean Yrs (SD)	BMI, Mean (SD), kg/m²	Weight, Mean (SD), kg	OA site, %		KLG in target joint, %			
						Knee	Hip	Grade 1	Grade 2	Grade 3	Grade 4
Barthel, et al., 2009[5], ITT	DSG (254)	32.7/67.3	59.7 (10.5)	30.9 (6.2)	87.5 (18.8)	100	-	-	-	-	-
	PBO (238)	33.5/65.5	59.2 (10.6)	31.8 (7.0)	90.0 (20.6)	100	-	-	-	-	-
Barthel, et al., 2009[5], MES population	DSG (127)	34.6/65.4	59.7 (10.8)	30.1 (6.4)	85.2 (19.6)	100	-	-	-	-	-
	PBO (119)	33.6/66.4	58.4 (10.4)	32.2 (7.1)	89.9 (20.9)	100	-	-	-	-	-
Baraf, et al., 2010[6]	DSG (208)	39.4/60.6	61.8 (10.9)	31.7 (6.8)	90.2 (20.7)	100	-	20.2	39.4	40.4	0
	PBO (212)	33.5/66.5	60.9 (10.9)	31.9 (7.3)	90.0 (21.5)	100	-	23.6	36.8	39.6	0
Altman, et al., 2007[8]	AER3900 (160)	28.8/71.3	61.7 (10.7)	34.1 (9.3)	208.2 (60.7) lbs	81.3	18.7	-	-	-	-
	AER1950 (158)	42.4/57.6	63.1 (10.9)	30.8 (6.2)	193.6 (44.6) lbs	81	19	-	-	-	-
	PBO (158)	28.5/71.5	61.8 (10.7)	33.2 (7.9)	202.7 (49.4) lbs	81.8	18.2	-	-	-	-
Prior, et al., 2014[7]	AER3900 (267)	22.5/77.5	61.7 (10.24)	---	197.3 (49.68) lbs	82	18	0	57.7	42.3	0
	PBO (275)	28.7/71.3	61.7 (10.05)	---	196.6 (49.2) lbs	81.8	18.2	0	57.5	42.5	0
Reed, et al., 2018[9]	ASR (224)	37.5/62.5	60.2 (8.4)	30.3 (4.8)	---	91.5	8.5	0	58.9	36,2	4.9
	AER3900 (225)	37.8/62.2	60.4 (8.5)	30.2 (4.7)	---	92	8	0	59.6	32	8.4
	PBO (227)	36.1/63.9	61.7 (8.2)	30.4 (4.8)	---	91.2	8.8	0	62.1	30.8	7

MES, modified efficacy subpopulation; **DSG**, diclofenac sodium 1% gel; **AER3900**, acetaminophen extended release 3900 mg; **AER 1950**, acetaminophen extended release 1950 mg; **ASR**, acetaminophen sustained release 2000 mg; **PBO**, placebo; **M**, male; **F**, female; **Yrs**, years; **SD**, standard deviation; **kg**, kilograms; **lbs**, pounds; **OA**, osteoarthritis; **KLG**, Kellgren Lawrence Grade

Endpoints

- ASR did not achieve statistically significant efficacy vs placebo for WOMAC pain, physical function or stiffness subscales.
- DSG 1% demonstrated statistically significant and clinically meaningful efficacy in all WOMAC subscales vs placebo.
- AER demonstrated statistically significant efficacy vs placebo in some WOMAC endpoints at 3900 mg/day, nearly the maximum daily limit for acetaminophen (4000mg/day).
- **% reduction from baseline vs placebo is approximately 1.5 times greater for DSG 1% than for AER (3900mg/day)**

Table 2. Percent improvement from baseline of WOMAC subscales at week 12.

DSG 1% (4g, QID)				
Barthel, et al., 2009, ITT[5] N = 492	**Mean %-change from baseline**		**p-value**	**D-P %**
	DSG (D) N = 254	**Placebo (P) N = 238**		
Pain	46	39	0.028	7
Function	42	32	0.002	10
Stiffness	NR	NR	NR	---
Barthel, et al., 2009, MES[5]* N = 246	**Mean %-change from baseline**		**p-value**	**D-P %**
	DSG (D) N = 127	**Placebo (P) N= 119**		
Pain	51	39	0.023	12
Function	47	31	0.003	16
Stiffness	48	30	0.001	18
Baraf, et al., 2010[6] N = 420	**Mean %-change from baseline**		**p-value**	**D-P %**
	DSG (D) N = 208	**Placebo (P) N = 212**		
Pain	53	43	0.008	10
Function	50	39	0.004	11
Stiffness	49	39	0.003	10
AER 3900 mg (1300mg, TID); AER 1950 mg (1 X 650 mg plus 1 placebo; TID)				
Altman, et al., 2007[8] N = 482	**Mean %-change from baseline**		**p-value**	**A-P %**
	AER 3900 (A) N = 160	**AER 1950 (A2) N = 158**	**Placebo (P) N = 165**	
Pain	38	34	30	0.012	8
Function	36	29	27	0.016	9
Stiffness	36	30	30	0.088	6
AER 3900 mg (1300mg, TID)				
Prior, et al., 2014[7] N = 542	**LS Mean %-change from baseline**		**p-value**	**A-P %**
	AER (A) N = 267	**Placebo (P) N = 275**		
Pain	38	32	0.054	6
Function	35	28	0.011	7
Stiffness	34	26	0.004	8
ASR 4000 mg (2000 mg, BID); AER 3900 mg (1300mg, TID)					
Reed, et al., 2018[9] N = 708	**LS Mean %-change from baseline**		**p-value S vs P**	**p-value A vs P**	**S-P %**
	ASR (S) N = 235	**AER (A) N = 236**	**Placebo (P) N = 237**		
Pain	41	38	36	0.163	0.935	5
Function	NR	NR	NR	0.089	0.673	---
Stiffness	NR	NR	NR	0.054	0.667	---

NR, not reported in publication; *Data on file

Safety

- In general, all treatments were well tolerated
- The percentage of patients reporting AE's was generally similar in all treatment groups within and between studies (40-60%), with the exception of the ASR[9] study, which had 21.5-29.2% of patients reporting AE's in each treatment group
- **The percentage of patients reporting Serious AEs was low in all studies (0-3%)**

Table 3. Summary of common Adverse Events.

Study	Treatment (n)	Event, n (%)						Treatment-related AE, n (%)		
		Any AE	Severe AE	Serious AE	Headache	Diarrhea	Nausea	Any	ALT and/or AST increase > 3 x ULN	Application site dermatitis
Barthel, et al., 2009[5]	DSG (254)	153 (60.2)	13 (5.1)	3 (1.2)	35 (13.8)	NR	NR	20 (7.7)	0	11 (4.3)
	PBO (238)	128 (53.8)	14 (5.9)	2 (0.8)	34 (14.3)	NR	NR	10 (4.2)	0	7 (2.9)
Baraf, et al., 2010[6]	DSG (208)	54.8	11 (5.3)	6 (2.8)	30 (14.4)	NR	NR	12 (5.8)	0	12 (5.8)
	PBO (212)	43.4	2 (0.9)	0	28 (13.2)	NR	NR	0	0	0
Altman, et al., 2007[8]	AER3900 (160)	71 (44.4)	NR	3 (1.9)	9 (5.6)	9 (5.6)	NR	13 (8.1)	3 (1.9)	0
	AER1950 (158)	71 (44.9)	NR	3 (1.9)	7 (4.4)	7 (4.4)	NR	15 (9.5)	0	0
	PBO (165)	66 (40.0)	NR	2 (1.2)	5 (3.0)	4 (2.4)	NR	8 (4.8)	0	0
Prior, et al., 2014[7]	AER3900 (267)	148 (55.4)	NR	8 (3.0)	43 (16.1)	14 (5.2)	19 (7.1)	43 (16.1)	7 (2.5)	0
	PBO (275)	159 (57.8)	NR	2 (0.7)	57 (20.7)	7 (2.5)	9 (3.3)	39 (14.2)	1 (0.004)	0
Reed, et al., 2018[9]	ASR (234)	67 (28.6)	4 (1.7)	4 (1.7)	5 (2.1)	6 (2.6)	8 (3.4)	19 (8.1)	6 (2.6)	0
	AER3900 (236)	69 (29.2)	7 (3.0)	5 (2.1)	5 (2.1)	7 (3.0)	5 (2.1)	16 (6.8	4 (1.7)	0
	PBO (237)	51 (21.5)	4 (1.7)	0	5 (2.1)	2 (0.8)	4 (1.7)	10 (4.2)	0	0

DSG, diclofenac sodium 1% gel; **AER3900**, acetaminophen extended release 3900 mg; **AER 1950**, acetaminophen extended release 1950 mg; **ASR**, acetaminophen sustained release 2000 mg; **PBO**, placebo; **NR**, not reported in publication; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal

Limitations

- AER studies used mixed OA population of 80-90% knee OA, 10-20% hip OA, whereas DSG studies evaluated knee OA only.
- This was a comparative review of published efficacy data for DSG, AER and ASR vs placebo. The treatments have not been evaluated in head-to-head studies.

Conclusions

- Both DSG and AER demonstrated efficacy in WOMAC endpoints in patients with knee OA.
- Topical DSG treatment provided clinically and statistically significant improvements in pain, function, and stiffness, which were noticeably greater than the results achieved with AER dosed at nearly the maximum daily limit for acetaminophen (3900mg, 4000mg daily maximum).
- Topical DSG 1% is be an appropriate option for patients with knee OA who desire effective local pain relief with minimal systemic NSAID exposure.
- These results should be considered by healthcare providers when recommending a treatment for symptoms of knee OA.

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