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Efficacy of Off-Label Topical Treatments for the Management of Androgenetic Alopecia: a Systematic Review

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Abstract

Androgenetic alopecia (AGA) is characterized by non-scarring follicle miniaturization. Despite the success of approved therapies, commonly reported side effects and the need for continual use has led to the investigation of alternative therapies. The aim of this paper is to critically review the success of off-label, topical monotherapies for treatment of AGA in men. A literature search was conducted to obtain randomized, controlled and blinded studies that investigated off-label, topical, monotherapies in male patients. Hair density, hair diameter and hair growth were used to evaluate treatment success. Fourteen off-label topical therapies were investigated among the 16 studies that met inclusion criteria. Nine off-label therapies were reported to produce a significantly greater improvement in hair restoration parameters (e.g., mean change from hair count and hair diameter) as compared to placebo ($p < 0.05$ for all treatments). In two studies, procyanidin oligomers exhibited greater efficacy over vehicle with response to mean change in hair density (hairs/cm²) ($p_s < 0.0001$ at week 24). In conclusion, prostaglandin analogs and polyphenols, such as latanoprost and procyanidin oligomers, can improve hair restoration parameters in male AGA patients, possibly through targeting mechanisms proposed in the etiology of AGA. The current evidence suggests short term (24 weeks) use may provide benefit for hair loss patients; however, long-term efficacy and safety data are required.

Key Points

- Due to the potential side effects and the need for continual use of approved therapies, there is a need to explore the efficacy of off-label options.
- Eight off-label topical therapies, including prostaglandin analogs and polyphenols, were found to improve hair density, while one additional therapy improved hair diameter.

Keywords: androgenetic alopecia, off-label therapies, prostaglandin analogs, polyphenols

1.0 Introduction

Androgenetic alopecia (AGA) is a common hair loss disorder characterized by non-scarring follicle miniaturization¹. The etiology of AGA is multifactorial and polygenetic, with androgens playing a pivotal role^{2,3}. Finasteride, an oral 5- α reductase inhibitor, and minoxidil, a topical vasodilator, are FDA and Health Canada approved for treatment of AGA⁴⁻⁷. Despite their success, these approved therapies have several drawbacks. Their improvement in hair restoration parameters tends to plateau after a few years of continued use. In addition, these approved therapies have been associated with side effects such as skin irritation and sexual dysfunction⁴⁻⁷. Thus, there is a need for new, safe and effective treatments for AGA. The aim of this paper is to critically review the success of off-label, topical therapies for treatment of androgenetic alopecia in men.

2.0 Methods of Literature Search

A literature search in PubMed, MEDLINE (Ovid), Embase (Ovid), and CINAHL was conducted using the following search terms: 'androgenetic alopecia', 'male pattern baldness', 'AGA' and 'randomized controlled trial' (February 2018). Randomized, controlled (placebo or vehicle) and blinded (single, double or triple) trials that investigated topical off-label monotherapies for the treatment of androgenetic alopecia in male patients were included. Studies that investigated oral or combination therapies, included only female patients, and/or included alopecia conditions other than androgenetic alopecia were excluded. Eligible studies were required to evaluate treatment success using hair density (hair/cm²), hair diameter (mm) or hair growth (mm/cm²). Clinical outcomes vary widely among studies; we selected a range of quantitative measurements to be as inclusive and objective as possible.

3.0 Results of Literature Search

Sixteen studies met inclusion criteria (Figure 1)⁸⁻²³. A total of 1,709 male participants were included with an average age of 40 years. Fourteen off-label topical therapies were investigated: a

penta-peptide (Gly-Pro-Ile-Gly-Ser), adenosine, bimatoprost, *Curcuma aeruginosa* extract, dabao, fulvestrant, a herbal extract, latanoprost, a non-steroidal anabolic hormone gel, procyanidin oligomers, pyridithione zinc, roxithromycin, sodium valproate and viprostal (Tables 1-3)⁸⁻²³. Treatment duration ranged from 4 weeks²³ to 52 weeks²¹ with 24 weeks the most common duration (10/16 = 63%)^{9,12,15-19,21-23}. Investigated therapies were administered in a wide array of formulations including cream (herbal extract¹¹), gel (non-steroidal anabolic hormones¹⁸), lotion (adenosine, penta-peptide, dabao, roxithromycin^{12-14,17}), shampoo (pyridithione zinc⁸), solution (bimatoprost²²⁻²³, latanoprost⁹, *Curcuma aeruginosa* extract²⁰, fulvestrant¹⁰, procyanidin^{16,21}, viprostal¹⁹), and spray (sodium valproate¹⁵).

3.1 Hair Density

Fifteen included studies used hair density to evaluate treatment success of off-label therapies in AGA patients^{8-11,13,15-23}. The mean change in hair density (hairs/cm²) from baseline to end of treatment for off-label therapies ranged from - 4 hairs/cm² to 54 hairs/cm² (Table 1). Eight off-label therapies (pyridithione zinc shampoo, latanoprost, a herbal extract, adenosine, sodium valproate spray, procyanidin oligomers, dabao, and a non-steroidal anabolic hormone solution) had a significantly higher mean change from baseline as compared to placebo ($p < 0.05$ for all treatments)^{8,9,11,13,15-18,21}. The highest mean change in hair density (hairs/cm²) after 24 weeks of treatment was found with latanoprost (Figure 2)⁹. Two studies reported procyanidin oligomer treatment exhibited greater efficacy over vehicle with response to mean change in hair density (hairs/cm²) by end of 24 weeks of treatment ($p_s < 0.001$)^{16,21}.

3.2 Hair Diameter

Two included studies used changes in hair diameter to evaluate treatment success of off-label therapies in AGA patients (Table 2)^{8,12}. Mean change in hair diameter (mm) as compared to baseline was significantly higher with roxithromycin as compared to vehicle after 24 weeks of treatment ($p < 0.01$)¹², whereas, 26 weeks of pyridithione zinc treatment was not significantly different from placebo treatment⁸.

3.3 Hair Growth

Three studies measured the impact of off-label topical therapy on mean change in hair growth, as defined as mm/cm² from baseline, compared to vehicle treated patients (Table 3)^{10,22,23}. Bimatoprost treatment once or twice a day produced a mean change in hair growth after 24 weeks of treatment of 0.76 mm/cm² and 0.92 mm/cm², respectively^{22,23}. A significantly lower mean change in hair growth was found with fulvestrant as compared to minoxidil after 16 weeks of treatment ($p < 0.001$)¹⁰.

4.0 Discussion

In recent years, many novel treatments for treating AGA and other hair loss have been investigated. The objective of this review was to evaluate therapeutic, off-label options available to treat AGA. The existing pharmaceutical therapies for AGA are oral finasteride and topical minoxidil; some of the off-label treatments discussed in this review work via similar mechanisms. Eight off-label therapies (pyrithione zinc shampoo, latanoprost, a herbal extract, adenosine, sodium valproate spray, procyanidin oligomers, dabao, a non-steroidal anabolic hormone solution) produced significant increases in hair density, while roxithromycin significantly increased hair diameter^{8,9,11-13,15-18,21}. Apart from placebo/vehicle, minoxidil 5% was used as an active comparator in three studies, where it was significantly better than fulvestrant¹⁰, numerically similar to pyrithione zinc shampoo⁸ and *C. aeruginosa* extract²⁰, and numerically better than bimatoprost formulations²². Although safety was not a focus of this review, all but four studies^{8,17-19} monitored adverse events. There were no adverse events or adverse events related to treatment for herbal extract, adenosine, procyanidin oligomers, and roxithromycin. Studies of bimatoprost, latanoprost, fulvestrant, herbal extract, valproate, and *Curcuma aeruginosa* reported mild skin-related adverse events such as erythema, pruritus, urticarial, or dermatitis. Most of the treatments appear to be well-tolerated and safe in the short-term.

Of the 24 week treatments, latanoprost, a prostaglandin analog antagonist, was found to have the highest mean change in hair density (hairs/cm²)⁹. Prostaglandin analogs, which include latanoprost, bimatoprost and viprostol, can stimulate keratinocyte and melanocyte activity, enhancing hair growth and pigmentation²⁴. Interestingly, viprostol, a synthetic prostaglandin inhibitor, was not an effective treatment¹⁹. This finding could be due to the synthetic nature of viprostol, the hair loss severity of included patients (IIIv to V) or the dosage used.

In two studies, procyanidin oligomers exhibited a greater efficacy over vehicle by end of treatment with response to mean change in hair density (hairs/cm²)^{16,21}. Procyanidin oligomers, and other polyphenols, most likely promote hair growth via nitric oxide, a gas produced in the lining of veins which promotes vasodilation and reduces cholesterol build-up. Polyphenols have also been shown to inhibit 5 α -reductase activity which has been theorized to play a role in the pathogenesis of AGA²⁵.

Regardless of these promising effects, more clinical trials need to be conducted before the use of these off-label treatments is sanctioned. Of particular note is that the current evidence for off-label treatments is from clinical studies that are short in duration, with 24 weeks the most common. Long-term efficacy and safety data are not available and we are thus unable to draw comparisons with approved therapies. While improvement can plateau over time with finasteride and minoxidil, the long-term efficacy of off-label treatments is unknown. The patients in the included studies were predominantly male and differences in treatment efficacy between males and females should be kept in mind. Therapies with multi-factorial capabilities may be more appropriate for treating female pattern hair loss, whereas, male pattern hair loss patients benefit more from a direct anagen effect².

Additionally, an important limitation when evaluating efficacy of hair loss treatments is the variety of outcome measures used to measure successful hair growth; there is no accepted industry standard. Assessment of global photographs by an expert, hair counts using phototrichogram, and

manual hair counts using clippings or hair density in a target area were all reported in studies. Global assessments based on photographs, for example, can offer useful insight, but they are not the same as blinded quantitative measurement. Hair count can be converted into hair density when a target area is provided by the authors, but not all authors disclosed this information. This should be a point of consideration in the development of new trials as a consistent quantitative outcome measure can aid in comparing different treatments. Patient-centred outcomes such as satisfaction are also important. While the reported data (Tables 1-3) certainly show an increase in hair parameters, increases may not be noticeable or satisfactory for patients to justify treatment or, patients may express satisfaction despite little to no clinical improvement. Even if patients believe a treatment is beneficial, a case can be made that clinicians should not encourage use of treatments that do not objectively improve hair loss.

5.0 Conclusion

Preliminary evidence suggests that, in the short-term, eight off-label therapies such as prostaglandin analogs and polyphenols can significantly improve hair density^{8,9,11,13,15-18,21}. Further study of hair loss patients enrolled in randomized, controlled and blinded studies is needed to expand on the efficacy and safety data that has been collected to date. In the meantime, clinicians may wish to use off-label therapies as they may provide benefit to patients. Hair loss needs should be addressed individually as both off-label and approved treatment that works for one person may not work for another.

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Figure Captions:

Figure 1: Study Selection Process

Figure 2: Mean Change in Hair Density (hairs/cm²) after 24 weeks of Off-Label Topical Therapy^{8,9,13-22}.

Bimatoprost A, B, and C: Details on these treatment groups (e.g., percentage of bimatoprost) not yet released on clinicaltrials.gov; **Dabao:** 50% ethanol, 42% water, 8% Chinese herbal extracts (saffron flowers, mulberry leaves, stemona root, fruits of the pepper plant, sesame leaves, the skin of the fruit of Sichuan pepper, ginger root, Chinese angelica root, bark of the Pseudolarix, fruits of the hawthorn); **Latanoprost:** 50% ethanol, 20% propylene glycol water; **Non-steroidal anabolic hormones (NSAH):** CMM, made of insulin, thyroxin and growth hormone gelled in 1.5% hydroxyethyl cellulose; **Procyanidin B-2:** 70% ethanol, 10% 1,3-butylene glycol, 0.5% N-acetylglutamine-isostearyl ester, 0.25%polyoxyethylene glyceryl monopyroglutamate monoisosterate, 0.1% dl- α -tocopherol, 0.05% d-biotin, 0.1% ascorbyl palmitate, 0.001% β -carotene, 0.1% sodium citrate and 17.899% purified water; **Procyanidin Mix:** 7.3% procyanidin B-1, 26.2% procyanidin B-2, 7.7% procyanidin C-1, 40% other oligomeric procyanidins, 70% ethanol, 3% 1,3-butylene glycol, 0.15% N-acetylglutamine isostearyl ester, 0.067% citrate-sodium citrate buffer, 0.05% sodium bisulfite, purified water; **Sodium Valproate:** 8.3% sodium valproate using a 27% ethanol solution as the vehicle.

Table 1: Impact of Off-Label Topical Therapy on Hair Density (hairs/cm²) by End of Treatment

Study	Characteristics	Treatment Details	Mean Change From Baseline
Berger et al. 2003 ⁸	N: 200 Age: 40 Severity: IIIv to IV Duration: 26 wks	Placebo Shampoo (1x day)	-1 hairs/cm ²
		Pyrrithione Zinc Shampoo (1%, 1x day)	6 hairs/cm ^{2*}
		Pyrrithione Zinc Shampoo (1%, 1x day) + Minoxidil (5%, 2x day)	6 hairs/cm ^{2*}
		Minoxidil (5%, 2x day) + Placebo Shampoo (1x day)	12 hairs/cm ^{2*}
Blume-Peytavi et al. 2012 ⁹	N: 16 Age: (23-35) Severity: II to III Duration: 24 wks	Placebo (50 µL/day)	8 hairs/cm ²
		Latanoprost (0.1%, 50 µL/day)	51 hairs/cm ^{2*}
Gassmueller et al. 2008 ¹⁰	N: 102 Age: 38 Severity: III to Va Duration: 16 wks	Vehicle (2x day)	8 hairs/cm ²
		Fulvestrant (70 mg/mL, 42 mg/day)	8 hairs/cm ²
		Minoxidil (20 mg/mL, 12 mg/day)	25 hairs/cm ^{2**}
Greenberg & Katz 1996 ¹¹	N: 24 Age: 43 Severity: III to IV Duration: 40 wks	Vehicle (1x day)	6 hairs/cm ²
		Herbal Extract (1x day)	54 hairs/cm ^{2*}
Iwabuchi et al. 2016a ¹³	N: 38 Age: 42 Duration: 24 wks	Vehicle	-10 hairs/cm ²
		Adenosine (0.75%)	12 hairs/cm ^{2*}
Jo et al. 2014 ¹⁵	N: 40 Age: 38 Severity: IIIv to V Duration: 24 wks	Vehicle (0.8 mL/dose, 2x day)	-1 hairs/cm ^{2a}
		Sodium Valproate Spray (0.8 mL/dose, 2x day)	23 hairs/cm ^{2a*}
Kamimura et al. 2000 ¹⁶	N: 30 Age: 47 Duration: 24 wks	Placebo (1%, 1.8 mL 2x day)	4 hairs/cm ²
		Procyanidin B-2 (1%, 1.8 mL 2x day)	28 hairs/cm ^{2*}
Kessels et al. 1991 ¹⁷	N: 396 Duration: 24 wks	Placebo (1.7 mL, 2x day)	22 hairs/cm ²
		Dabao (1.7 mL, 2x day)	27 hairs/cm ^{2*}
Lindenbaum et al. 2003 ¹⁸	N: 56 Age: 28 Severity: II to IV Duration: 24 wks	Placebo (1-3 mL/day)	16 hairs/cm ²
		Non-Steroidal Anabolic Hormones (1-3 mL/day)	30 hairs/cm ^{2*}
NCT01325337 ²²	N: 307 Duration: 24 wks	Vehicle (1x day)	4 hairs/cm ^{2b}
		Bimatoprost Formulation B (1x day)	6 hairs/cm ^{2b}
		Bimatoprost Formulation C (1x day)	6 hairs/cm ^{2b}
		Bimatoprost Formulation A (1x day)	13 hairs/cm ^{2b}
		Minoxidil (5%, 1x day)	22 hairs/cm ^{2b}
NCT01904721 ²³	N: 244 Duration: 7-24 wks	Bimatoprost Solution 1 (2x day)	13 hairs/cm ^{2b}
		Bimatoprost Solution 2 (2x day)	9 hairs/cm ^{2b}
		Vehicle (2x day)	6 hairs/cm ^{2b}
Olsen & DeLong et al. 1990 ¹⁹	N: 72 Age: 38 Severity: IIIv to V Duration: 24 wks	Vehicle (0.3 mL/dose, 2x day)	-8 hairs/cm ²
		Viprostol (120 µg, 0.3 mL/dose, 2x day)	-4 hairs/cm ²
		Placebo (0.3 mL/dose, 2x day)	-3 hairs/cm ²
Pumthong et al. 2012 ²⁰	N: 89 Age: 39 Severity: II-VII Duration: 24 wks	Vehicle (2x day)	20 hairs/cm ²
		<i>Curcuma aeruginosa</i> extract (5%, 2x day)	31 hairs/cm ²
		Minoxidil (5%, 2x day)	31 hairs/cm ²
		Minoxidil (5%, 2x day) + <i>Curcuma aeruginosa</i> extract (5%, 2x day)	33 hairs/cm ²
Takahashi et al. 2005 ²¹	N: 49 Age: (27-58) Duration: 24-52 wks	Vehicle (2 mL 2x day)	-8 hairs/cm ²
		Procyanidin (0.7%, 2 mL 2x day)	6 hairs/cm ^{2*}

*p<0.05 as compared to placebo / vehicle; **p<0.05 as compared to comparator; a: median change; b: terminal hairs were used; **Age (years)**: Mean (range); **Severity**: Based on Hamilton-Norwood Scale and eligibility criteria; **Wks**: weeks; **Latanoprost**: 50% ethanol, 20% propylene glycol water; **Herbal extract**: 7.5% extract of fennel,

polygonum, mentha, chamomile, thuja and hibiscus in a water-based cream; **Sodium Valproate Spray:** 8.3% sodium valproate using a 27% ethanol solution as the vehicle; **Procyanidin B-2:** 70% ethanol, 10% 1,3-butylene glycol, 0.5% N-acetylglutamine-isostearyl ester, 0.25%polyoxyethylene glyceryl monopyroglutamate monoisosterate, 0.1% dl- α -tocopherol, 0.05% d-biotin, 0.1% ascorbyl palmitate, 0.001% β -carotene, 0.1% sodium citrate and 17.899% purified water; **Procyanidin:** 7.3% procyanidin B-1, 26.2% procyanidin B-2, 7.7% procyanidin C-1, 40% other oligomeric procyanidins, 70% ethanol, 3% 1,3-butylene glycol, 0.15% N-acetylglutamine isostearyl ester, 0.067% citrate-sodium citrate buffer, 0.05% sodium bisulfite, purified water; **Dabao:** 50% ethanol, 42% water, 8% Chinese herbal extracts (saffron flowers, mulberry leaves, stemona root, fruits of the pepper plant, sesame leaves, the skin of the fruit of Sichuan pepper, ginger root, Chinese angelica root, bark of the Pseudolarix, fruits of the hawthorn); **Non-steroidal anabolic hormones:** CMM, made of insulin, thyroxin and growth hormone gelled in 1.5% hydroxyethyl cellulose; **Bimatoprost A, B, C, 1 and 2:** Details on these treatment groups (e.g., percentage of bimatoprost) not yet released on clinicaltrials.gov

Table 2: Impact of Off-Label Topical Therapy on Hair Diameter (mm) by End of Treatment^{8,14}

Study	Characteristics	Treatment Details	Mean Change from Baseline
Berger et al. 2003 ⁸	N: 200 Age: 40 Severity: IIIv to IV Duration: 26 wks	Placebo Shampoo (1x day)	-0.04 mm
		Pyrrithione Zinc Shampoo (1%, 1x day)	-0.04 mm
		Pyrrithione Zinc Shampoo (1%, 1x day) + Minoxidil (5%, 2x day)	-0.01 mm
		Minoxidil (5%, 2x day) + Placebo Shampoo (1x day)	-0.01 mm
Ito et al. 2009 ¹²	N: 24 Age: 48 Severity: II to IIIIV Duration: 24 wks	Vehicle	0.0004 mm
		Roxithromycin	0.309 mm*
*p<0.01 as compared to baseline; Age (years) : Mean (range); Severity : Based on Hamilton-Norwood Scale and eligibility criteria; Wks : weeks; Roxithromycin : 0.5% Roxithromycin, 65% ethyl alcohol, 5% propylene glycol, 39.5% distilled water			

Table 3: Impact of Off-Label Topical Therapy on Hair Growth (mm/cm²) by End of Treatment^{10,24,25}

Study	Characteristics	Treatment Details	Mean Change from Baseline
Gassmueller et al. 2008 ¹⁰	N: 102 Age: 38 Severity: III to Va Duration: 16 wks	Vehicle (2x day)	0.7 mm/cm ²
		Fulvestrant (70 mg/mL, 42 mg/day)	0.84 mm/cm ²
		Minoxidil (20 mg/mL, 12 mg/day)	2.9 mm/cm ² *, ^
NCT01325337 ²²	N: 307 Duration: 24 wks	Bimatoprost Formulation C (1x day)	0.12 mm/cm ²
		Vehicle (1x day)	0.13 mm/cm ²
		Bimatoprost Formulation B (1x day)	0.25 mm/cm ²
		Bimatoprost Formulation A (1x day)	0.76 mm/cm ²
		Minoxidil (5%, 1x day)	1.29 mm/cm ²
NCT01904721 ²³	N: 244 Duration: 7-24 wks	Vehicle (2x day)	0.05 mm/cm ²
		Bimatoprost Solution 2 (2x day)	0.67 mm/cm ²
		Bimatoprost Solution 1 (2x day)	0.92 mm/cm ²
*p<0.05 as compared to placebo / vehicle; ^p<0.05 as compared to investigated off-label topical therapy; Age (years) : Mean; Severity : Based on Hamilton-Norwood Scale and eligibility criteria; Wks : weeks; Bimatoprost A, B, C, solution 1 and solution 2 : Details on these treatment groups (e.g., percentage of bimatoprost) not yet released on clinicaltrials.gov			

Figure 1.

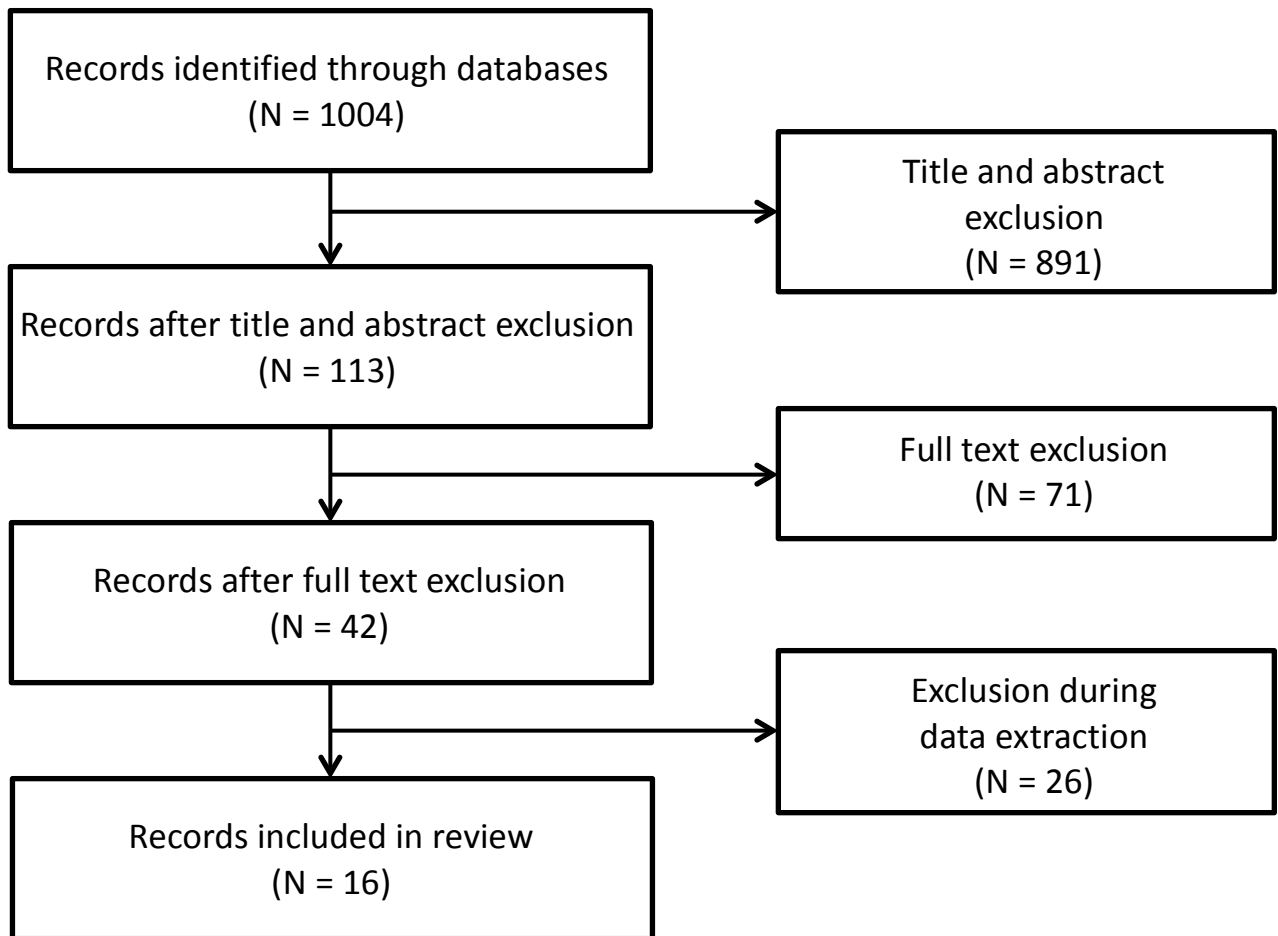


Figure 2

