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Soft Computing Approach on drug Management for Hypertensive Patients with Chronic Kidney Disease.

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ABSTRACT

In this paper, we propose a soft computing approach for drug management of hypertensive patients with Chronic Kidney Disease (CKD). Hypertension is a common risk factor to patients with CKD as it exposes them to fast progression of renal damage. The application of expert systems in medical decision support had improved the ability to handle uncertainties, complexity and high variations existing in the medical data when compared with manual decision support systems. The key goal in the management of patient with CKD is to control the Blood Pressure (BP) and minimize proteinuria. This work apply soft computing technique in the design of a system based on antihypertensive agents needed for the management of hypertensive patients with CKD while using ACE inhibitors, Beta blockers, Diuretics and CKD stages as input parameters.

Keywords: Hypertension, Chronic Kidney Disease, Soft Computing, Expert system, decision support system.

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1. INTRODUCTION

The task of carrying out an effective management of hypertensive patient with CKD in order to delay the progression of renal damage is cumbersome. Hypertension in CKD increases the risk and promotes the adverse effects of loss of kidney function. The prevalence of hypertension continues to increase in aging and obese individuals. The pathophysiology of hypertensive renal damage suggests that therapeutic intervention should aim to reduce Blood Pressure (BP) load and also reduce the transmission of pressure to the renal microvasculature. It has been suggested that antihypertensive drugs should be chosen to control BP according to the new guideline to minimize proteinuria [1]. Considering the growing burden of hypertensive patients with CKD, and the limited primary health care providers delivering the majority of care; the implementation of a clinical decision support system would be relevant in improving the drug management of such conditions [2]. The health of population, which is based primarily on the result of medical research, has a strong impact upon all human activities [3].

Soft Computing techniques such as Artificial Neural Networks and Fuzzy Expert System offer the possibility of combining domain knowledge and data-driven adaptation capability in building intelligent models on drug dosage management which allows for a desired drug concentration regimen [4]. This technique have been successfully applied in solving problems related to drug management such as the model for the control of erythropoietin using a Bayesian approach [5]. [6] investigated the prescription of drugs among hospitalized patients with impaired renal function in electronic prescription, [7] presented a fuzzy logic-based approach for automation of drug delivery in renal failure while [8] presented a fuzzy inference model on drug dosing requirement for hypoglycaemic patient with CKD. In this paper, we present a soft computing approach on drug management for hypertensive patients with CKD.

2. OVERVIEW OF DOSAGE

To determine the dosage requirement in hypertensive patient with CKD, we first identify the drug dosage management in hypertensive patient with CKD [9]. The classes of drug used in this research are given in table 1 while table 2 presents the CKD classification.

Table 1: Antihypertensive Agents and usual dosage (Source: [10], [11])

Class	*Drug*	Usual dosage
ACE inhibitors	Benazepril	10mg daily
	Captopril	25mg every 8 hours
	Enalapril	5 to 10 mg every 12 hours
	Fosinopril	10mg daily
	Lisinopril	5mg daily
	Quinapril	20mg daily
	Ramipril	5mg daily
Beta blockers	Acebutolol	400mg once or twice daily
	Atenolol	100 mg daily
	Bisoprolol	10 mg daily
	Nadolol	80mg daily
Diuretics	Amiloride	5mg daily
	Spironolactone	100mg daily
	Thiazides	50 mg daily
	Triamterene	100mg twice daily

Table 2: CKD classification (Source: [12])

CKD Stages	**Description**	**GFR (ML/ Min/1.73m^2)**
1	**Normal/raised**	**≥ 90**
2	**Mild**	**60-89**
3	**Moderate**	**30-59**
4	**Severe**	**15-29**
5	**ESRD**	**< 15**

Table 3: Dosage adjustment for hypertensive patient with CKD

Drugs	**Normal/raised CKD-1**	**Mild CKD-2**	**Moderate CKD-3**	**Severe CKD-4**	**ESRD CKD-5**
Benazepril	No adjustment	No adjustment	7.5mg	5mg	2.5mg
Captopril	No adjustment	No adjustment	7.5mg	7.5mg	5mg
Enalapril	No adjustment	No adjustment	10mg	7.5mg	5mg
Fosinopril	No adjustment	No adjustment	10mg	10mg	7.5mg
Lisinopril	No adjustment	No adjustment	4mg	2.5mg	1.3mg
Quinapril	No adjustment	No adjustment	20mg	15mg	15mg
Ramipril	No adjustment	No adjustment	4mg	2.5mg	1.3mg
Acebutolol	No adjustment	No adjustment	300mg/daily	300mg/daily	180mg/daily
Atenolol	No adjustment	No adjustment	50mg/daily	50mg/daily	25mg/daily
Bisoprolol	No adjustment	No adjustment	7.5mg/daily	7.5mg/daily	5mg/daily
Nadolol	No adjustment	No adjustment	40mg/daily	40mg/daily	20mg/daily
Amiloride	No adjustment	No adjustment	2.5mg/daily	2.5mg/daily	-
Spironolactone	No adjustment	No adjustment	50mg/12hourly	50mg/12hourly	-
Thiazides	No adjustment	No adjustment	25mg/daily	25mg/daily	-
Triamterene	No adjustment	No adjustment	100mg/2xdaily	100mg/2xdaily	-

Table 1 shows the Antihypertensive Agents and its usual dosage for hypertensive patient without CKD which does not require adjustment in dosage regimen. Antihypertensive agents are renal cleared hence the need to appropriately adjust drug dosing for patient with CKD based on CKD stages. The classification of CKD is shown on table 2 while the adjusted dosage is reflected on table 3 and shows the different classes of Antihypertensive Agents with various drugs and its dosage adjustment in accordance with CKD stages.

3. DESIGN AND IMPLEMETATION

The system was designed using three classes of antihypertensive agents which include ACE inhibitors, Beta blocker and Diuretics. The knowledge base is composed of fifteen antihypertensive drugs and five stages for classification of CKD. The sets of drugs and CKD stages were fed into the system while the system carried out the dosage adjustment in accordance with the stages of CKD.

This is just as set in the rule base in knowledge repository. A fuzzy rule-based drug management system that utilizes the suggested method for dosage adjustments and management in hypertensive patient with CKD is presented at this juncture. The fuzzy set a in A (a universe of discourse) of hypertensive patient with CKD attributes denoted by x is given as equation (1).

$a = (x,\mu_a(x))/\ x\varepsilon A\ \mu_a(x)\varepsilon\ [0,1]$.....(1)

Where $\mu_a(x)$ is the membership function (MF) of x in a, and μ_a is the degree of membership of x in a in the internal [0, 1]. MF is of different types, commonly used MF are Triangular, Trapezoidal and Gaussian [13]. Triangular MF has been used in this work because of its success and extensive use in medical diagnosis due to its computational efficiency in modeling human reasoning process. Equation (2) shows the MF used in designing the Fuzzy system.

$$\mu_a(x)\begin{cases} 0 & \text{if } x \le b \\ \dfrac{x-a}{b-a} & \text{if } a \le x \le b \\ \dfrac{c-x}{c-b} & \text{if } b \le x \le c \\ 0 & \text{if } c \le x \end{cases} \quad \text{.....(2)}$$

An architectural model proposed for the system to determine drug dosing and management in hypertensive patient with CKD is shown in Figure 1.

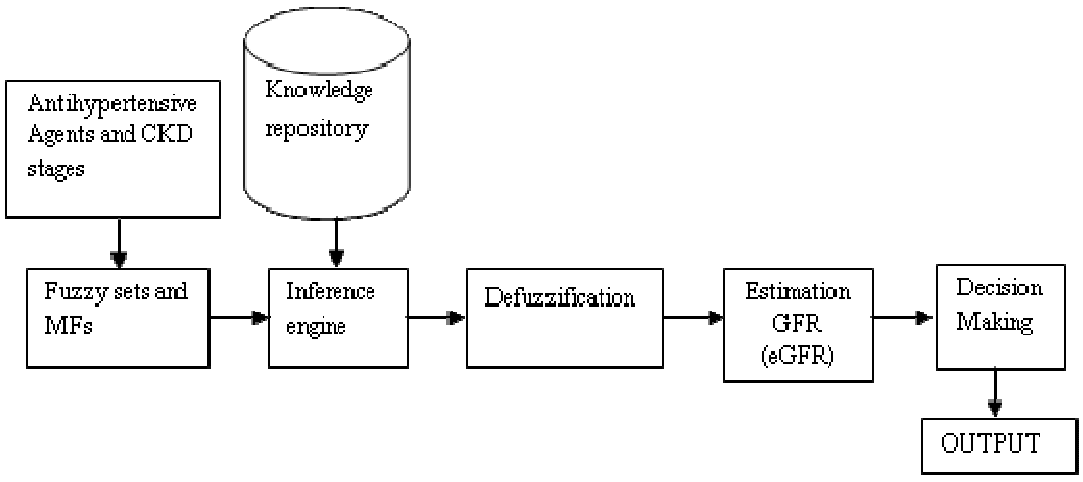

Figure 1: Proposed Architecture of the system

The system was modelled using an ordered set of rules in the following phases. The knowledge used in modelling the system was provided by experts based on recommended standard in drug dosage management for hypertensive patients with CKD using KDIGO guidelines [2]. The knowledge repository provided the quantitative and qualitative variables with Glumera Filtration Rate (GFR) classification. The inference engine consists of reasoning algorithm driven by rules. These rules were developed using forward chaining approach of reasoning and is stated hereunder:

ACE inhibitors:

Benazepril (Ben) Agent
Rule 1: IF GFR = 60 ≥ 90 THEN Usual dosage (10mg daily)
Rule 2: IF GFR = 30 ≥ 59 THEN Adjust Ben to 7.5mg daily
Rule 3: IF GFR = 15≥ 29 THEN Adjust Ben to 5mg daily
Rule 4: IF GFR < 15 THEN Adjust Ben to 2.5mg daily

Captopril (Cap) Agent
Rule 5: IF GFR = 60 ≥ 90 THEN Usual dosage (10mg 8 hourly)
Rule 6: IF GFR = 30 ≥ 59 THEN Adjust Cap to 7.5mg 8 hourly
Rule 7: IF GFR = 15≥ 29 THEN Adjust Cap to 7.5mg 8 hourly
Rule 8: IF GFR < 15 THEN Adjust Cap to 5mg 8 hourly

Enalapril (Ena) Agent
Rule 9: IF GFR = 60 ≥ 90 THEN Usual dosage (10mg 12 hourly)
Rule 10: IF GFR = 30 ≥ 59 THEN Adjust Ena to 7.5mg 12 hourly
Rule 11: IF GFR = 15≥ 29 THEN Adjust Ena to 7.5mg 12 hourly
Rule 12: IF GFR < 15 THEN Adjust Ena to 5mg 12 hourly

Fosinopril (Fos) Agent
Rule 13: IF GFR = 60 ≥ 90 THEN Usual dosage (10mg daily)
Rule 14: IF GFR = 30 ≥ 59 THEN Adjust Fos to 10mg daily
Rule 15: IF GFR = 15≥ 29 THEN Adjust Fos to 10mg daily
Rule 16: IF GFR < 15 THEN Adjust Fos to 7.5mg daily

Lisinopril (Lis) Agent
Rule 17: IF GFR = 60 ≥ 90 THEN Usual dosage (5mg daily)
Rule 18: IF GFR = 30 ≥ 59 THEN Adjust Fos to 4mg daily
Rule 19: IF GFR = 15≥ 29 THEN Adjust Fos to 2.5mg daily
Rule 20: IF GFR < 15 THEN Adjust Fos to 1.3mg daily

Quinapril (Qui) Agent
Rule 21: IF GFR = 60 ≥ 90 THEN Usual dosage (20mg daily)
Rule 22: IF GFR = 30 ≥ 59 THEN Adjust Fos to 20mg daily
Rule 23: IF GFR = 15≥ 29 THEN Adjust Fos to 15mg daily
Rule 24: IF GFR < 15 THEN Adjust Fos to 15mg daily

Ramipril (Ram) Agent
Rule 21: IF GFR = 60 ≥ 90 THEN Usual dosage (5mg daily)
Rule 22: IF GFR = 30 ≥ 59 THEN Adjust Ram to 4mg daily
Rule 23: IF GFR = 15≥ 29 THEN Adjust Ram to 2.5mg daily
Rule 24: IF GFR < 15 THEN Adjust Ram to 1.3mg daily

Beta blockers:

Acebutolol (Ace) Agents
Rule 25: IF GFR = 60 ≥ 90 THEN Usual dosage (400mg once or twice daily)
Rule 26: IF GFR = 30 ≥ 59 THEN Adjust Ace to 300mg once or twice daily
Rule 27: IF GFR = 15≥ 29 THEN Adjust Ace to 300mg once or twice daily
Rule 28: IF GFR < 15 THEN Adjust Ace to 180mg once or twice daily

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Atenolol (Ate) Agent
Rule 29: IF GFR = 60 ≥ 90 THEN Usual dosage (100mg daily)
Rule 30: IF GFR = 30 ≥ 59 THEN Adjust Ate to 50mg daily
Rule 31: IF GFR = 15≥ 29 THEN Adjust Ate to 50mg daily
Rule 32: IF GFR < 15 THEN Adjust Ate to 25mg once daily

Bisoprolol (Bis) Agent
Rule 33: IF GFR = 60 ≥ 90 THEN Usual dosage (10mg once daily)
Rule 34: IF GFR = 30 ≥ 59 THEN Adjust Bis to 7.5mg once daily
Rule 35: IF GFR = 15≥ 29 THEN Adjust Bis to 7.5mg once daily
Rule 36: IF GFR < 15 THEN Adjust Bis to 5mg daily

Nadolol (Nad) Agent
Rule 37: IF GFR = 60 ≥ 90 THEN Usual dosage (80mg once daily)
Rule 38: IF GFR = 30 ≥ 59 THEN Adjust Nad to 40mg once daily
Rule 39: IF GFR = 15≥ 29 THEN Adjust Nad to 40mg once daily
Rule 40: IF GFR < 15 THEN Adjust Nad to 20mg daily

Diuretics:
Amiloride (Ami) Agent
Rule 41: IF GFR = 60 ≥ 90 THEN Usual dosage (5mg once daily)
Rule 42: IF GFR = 30 ≥ 59 THEN Adjust Ami to 2.5mg once daily
Rule 43: IF GFR = 15≥ 29 THEN Adjust Ami to 2.5mg once daily
Rule 44: IF GFR < 15 THEN avoid Ami

Spironolactone (Spi) Agent
Rule 45: IF GFR = 60 ≥ 90 THEN Usual dosage (100mg 12hourly)
Rule 46: IF GFR = 30 ≥ 59 THEN Adjust Spi to 50mg 12hourly
Rule 47: IF GFR = 15≥ 29 THEN Adjust Spi to 50mg 12hourly
Rule 48: IF GFR < 15 THEN avoid Spi

Thiazides (Thi) Agent
Rule 49: IF GFR = 60 ≥ 90 THEN Usual dosage (50mg daily)
Rule 50: IF GFR = 30 ≥ 59 THEN Adjust Thi to 25mg daily
Rule 51: IF GFR = 15≥ 29 THEN Adjust Thi to 25mg daily
Rule 52: IF GFR < 15 THEN avoid Thi

Triamterene (Tri) Agent
Rule 49: IF GFR = 60 ≥ 90 THEN Usual dosage (100mg twice daily)
Rule 50: IF GFR = 30 ≥ 59 THEN Adjust Tri to 50mg twice daily
Rule 51: IF GFR = 15≥ 29 THEN Adjust Tri to 50mg twice daily
Rule 52: IF GFR < 15 THEN avoid Tri

The fuzzy rules on drug management for Hypertensive patients with CKD as given above has membership function degree within the interval (0, 1) and was gotten from real world dataset to fuzzy data by using minimum- maximum normalization equation as given in equation 3 below while table 4 shown the fuzzified data for adjusted dose management using Beta blocker agents.

$X_{ni} = \underline{X_1 - X_{MIN}}$ ……………………………………………………(3)

Where
X_{ni} = scaled input of real world
X_{min} = minimum values of unscaled dataset
Xmax = maximum values of unscaled dataset

Table 4: Fuzzified data for adjusted dose management

CKD Stages	DRUGS			
	Acebutolol	Atenolol	Bisoprolol	Nadolol
CKD-1	1	1	1	1
CKD-2	1	1	1	1
CKD-3	0.75	0.5	0.75	0.5
CKD-4	0.45	0.25	0.5	0.25

The Defuzzification process produced a quantifiable result for the given fuzzy sets and the corresponding membership degrees.

The program developed has several interfaces with varied functionalities. Firstly, it requires that the user or administrator login into the program in order to check that only authorised users have access to the system. This is shown in figure 2. Other aspects of the program perform patients registration given in figure 3, while figure 4 and figure 5 shows the CKD and Hypertension record form and prescription form respectively.

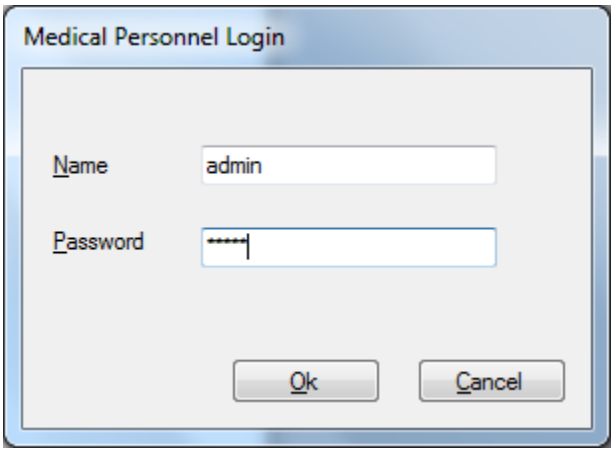

Figure 2: Admin login form

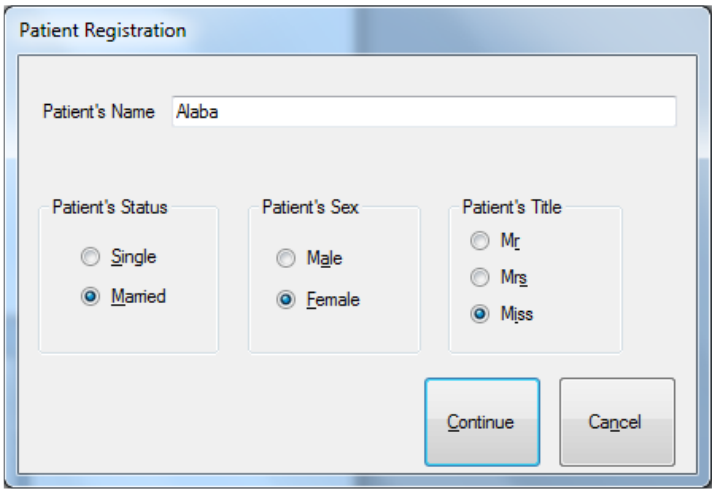

Figure 3: Patient registration form

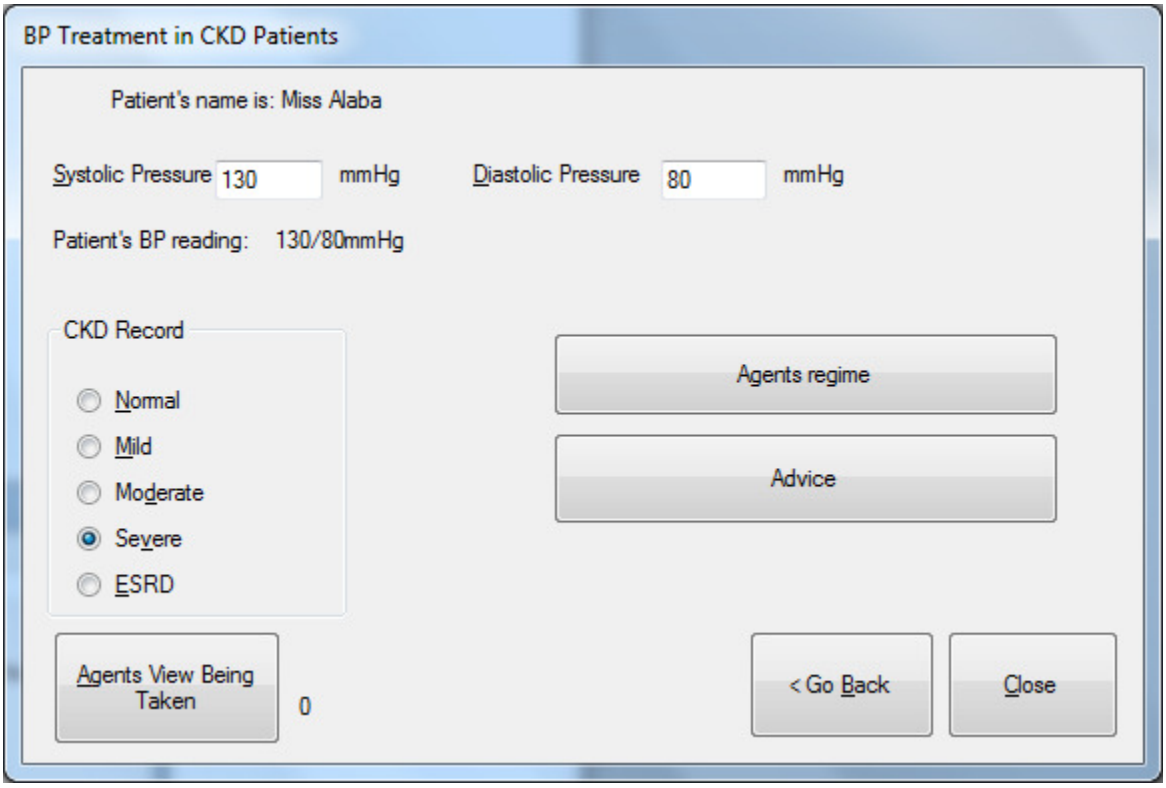

Figure 4: CKD and Hypertension record form

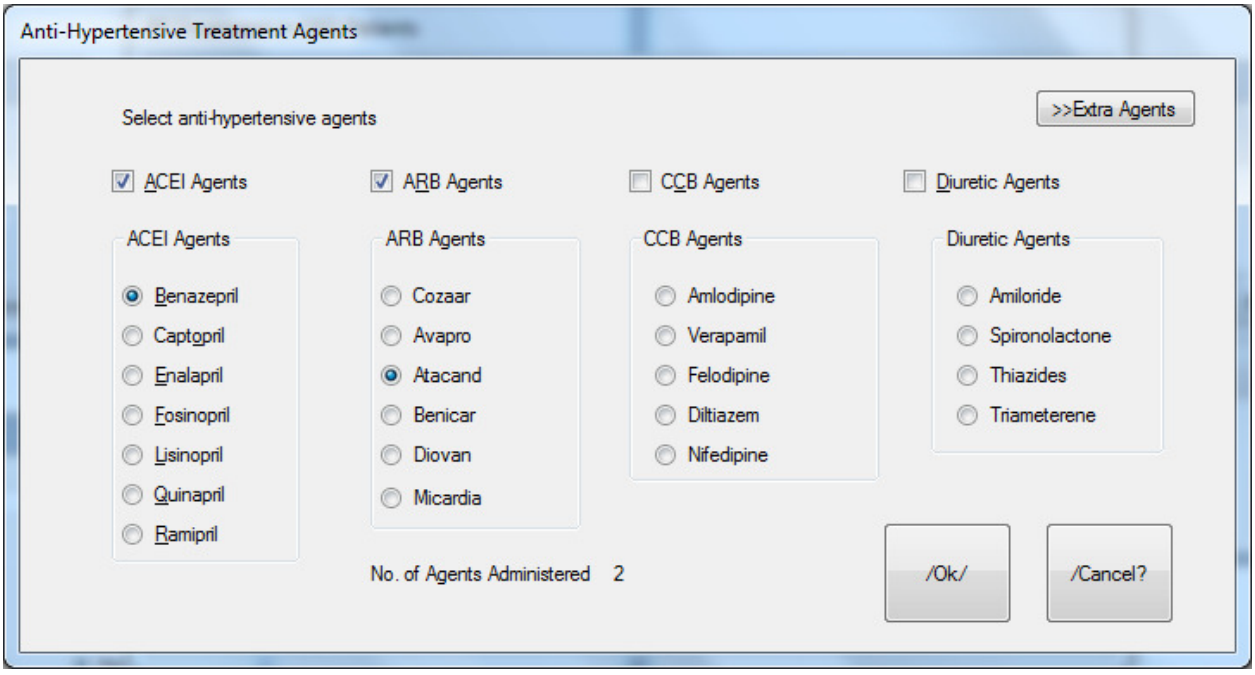

Figure 5: Prescription form

4. CONTRIBUTIONS TO KNOWLEDGE

This paper presented a soft computing approach for drug management of hypertensive patients with Chronic Kidney Disease (CKD). It provides an expert system for decision making with the goal of managing patients with CKD by controlling the Blood Pressure (BP) and minimize proteinuria.

5. CONCLUSION

A Soft Computing Approach on drug Management for Hypertensive Patients with Chronic Kidney Disease has been developed. This approach combines experience and patient data to develop a model for drug management and delivery combined with rule-based approach for different drug in antihypertensive patients with Chronic Kidney Disease (CLD)

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